CHEMOTHERAPY OF PSYCHIATRIC DISORDERS

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Chemotherapy of Psychiatric Disorders

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INTRODUCTION

It was both my good and bad fortune to have spent the first few years in psychiatry when, apart from psychotherapy and psychoanalysis, which was largely the same as we still know it today, paraldehyde, medinal, bromides and hot and cold baths were our main treatment weapons in mental illness. What horrifying days they were, and how few patients we could really help in their terrible and prolonged agony of mind!

On saying to a Maudsley colleague in 1936 that one day a book on the medical treatment of mental illness must be written, it was thought to be a very strange idea I was told sarcastically by him that the sum total of our medical knowledge on physical psychiatric treatment could be written on one thumbnail.

And so it was in those days. But now, thirty years later, we see the wish coming true. Dr. Peter Dally is now able to write a book on the medical use of drugs in psychiatry, and this approach can now really help so many of the mentally ill, especially those of good previous personality.

This is a most exciting book. The advances in physical treatment have made so many of the psychiatrically ill able at last to be treated quite simply by their general practitioners, especially if they use the detailed guidance given in this book. And many psychiatrists too will be grateful to Dr. Dally for letting us read about drug treatment as practised at the bedside and based on his own large personal experience, rather than his having to rely too much on the confusion of theories and differing views of other workers in this field.

I personally believe that Dally has exaggerated some of the potential dangers of the use of these drugs. But he stresses the need for courage, really skilled use, and the avoiding of all possible complications, when so much is at stake for the patient and his family; and if the illness is not quickly dealt with and brought under drug control.

We are now in the middle of a revolution in treatment in psychiatry. We are also only at the end of the beginning of the skilled use of an ever-increasing range of valuable drugs. We shall undoubtedly lose many of our patients back to general physicians and general practitioners if the instructions in the book are carefully followed. But there is so much neurosis and psychosis about that we

shall still all be overworked for years to come. The author will also have his work cut out in keeping the book up to date, based on his clinical and bedside findings, and helping us to keep in practical perspective the ever-growing drug literature which can be so confusing unless sorted out by personal skilled use.

We hope that this will be the first of many future editions.

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CHAPTER I

GENERAL INTRODUCTION

HISTORICAL DEVELOPMENT

There have been great changes in the treatment of psychiatric disorders over the past thirty years. Insulin coma therapy and convulsive therapy were introduced in the decade preceding World War II and rapidly transformed the outlook for patients with schizophrenia and depressive illnesses. Leucotomy began to be used increasingly. The value of abreaction, of deep sleep and complete rest, and restoration of weight and nutrition became recognised. And after the war a series of powerful new drugs began to appear, the psychotropic drugs, which make up what has been called "the chemical revolution" of psychiatry.

Even before the advent of the new psychotropic drugs, conditions in mental hospitals had begun to change, and a more active therapeutic regime to manifest itself. The work of Freud and his colleagues from the end of the last century had thrown new light upon character formation and focused attention upon the part played by environmental influences in bringing about and modifying emotional disorders. A more humane and sympathetic attitude towards mental patients slowly developed among doctors and public. Patients were seen to be as much in need of kindly human attention and companionship as their more fortunate and healthy fellows. "Chemical strait-jackets", induced by over-sedation with drugs like paraldehyde, chloral or bromide began to disappear. Wards were unlocked and a sense of self and mutual respect began to develop amongst staff and patients. Therapeutic enthusiasm grew and spread. Patients were encouraged at work and play, given more responsibility and freedom, and helped to feel that they were part of society and not outcasts. The concept of the therapeutic community, which had begun to develop a hundred years earlier but had come to a halt among the vast new Victorian mental hospitals, was thus rediscovered and added greatly to the effectiveness of psychiatric treatment.

It was into this therapeutically enthusiastic milieu that the modern psychotropic drugs were launched. At once they helped to accelerate the social and therapeutic changes occurring within the mental hospitals and the changing public attitudes towards mental illness.

Disturbed behaviour could now quickly be controlled and patients could be made more receptive to psychotherapy and social therapies. The total personality deterioration long regarded as the end result of schizophrenia but due in fact to the dulling effects of years of hospitalisation, so-called institutional neurosis, was now seen to be largely avoidable with a more active hospital regime.

Recent discoveries

Effective chemical treatment of serious psychiatric disorders involves the use of drugs which have in the main appeared over the past fifteen years and have replaced most of the older drugs like morphine, bromide and hyoscine. Of drugs in common usage more than thirty years ago only the barbiturates have survived the test of time. But it is salutary to remember that the historical roots of chemotherapy go deep and that substances capable of producing stimulation or sedation, of altering mental states and levels of consciousness, have long been known to man, even in the most primitive cultures.

For instance, the root of *rauwolfia serpentia* has been used for centuries in India as a sedative and a cure for insanity, although it was only in 1952 that the active alkaloid reserpine was isolated. And there are many accounts of the remarkable abilities of witch doctors and their like to cure abnormal mental states rapidly by means of secret potions which it would be foolish to regard as being due simply to suggestion and faith. Pizzaro in 1533 noticed that coca leaves were chewed by the Indians of Peru as a euphoriant, but not until 1885 was the active element in the leaves, cocaine, isolated from them. Various hallucinogenic substances were long used by the Aztecs and other pre-Columbian cultures of America to induce mystical and religious states, but it was only at the end of the last century that mescalin was isolated from the dumpling cactus and shown to be the active principle of peyotl.

However, most of our present day drugs have been discovered by chance rather than as a result of systematic investigation of a natural remedy or substance known to alter behaviour and mood. Psychiatry is now in a somewhat similar position to general medicine as it was a hundred years or so ago in having available effective but empirical methods of treatment whose mode of action is largely unknown.

In 1952 chlorpromazine, the first of the major tranquillisers, appeared and within a few years had virtually replaced deep insulin coma in the treatment of schizophrenia, and provided an effective means of controlling disturbed psychotic patients. The antidepressant drugs were introduced in 1957, and although they have not abolished the need for electroconvulsive therapy (ECT), they have altered treatment methods and outlook in depressive illnesses. Apart from

their therapeutic effects the psychotropic drugs have stimulated a vast amount of pharmacological and clinical research into their mode of action and the causes of mental disorders.

But this therapeutic revolution, splendid though it is, has produced its own problems. What drug is to be used for this or that type of patient? Which of the score or so of phenothiazine derivatives is most effective in this or that psychotic condition? What is the best dosage? What are the side effects? What of synergism or antagonism when two or more drugs are combined? No one clinician can possibly have wide experience and understanding of all these new drugs, and it is the exception, all too often, for the numerous and frequently contradictory reports of new drug trials to offer him much help in this respect.

SPECIFIC AND NON-SPECIFIC DRUG EFFECTS

How do these new drugs act? We know about some of their actions, but we do not know whether they act on the basic abnormalities presumed to underlie psychiatric illnesses, or only at some intermediate level. Some authorities even deny that these drugs have any specific action at all and claim that they are no better in their effects than placebos. But this is to confuse specific with non-specific (placebo) drug effects. Forceful suggestion is certainly a powerful tool, although more so with neurotic than psychotic patients. But while a depressed patient may initially respond to a dummy tablet in hospital (the placebo improvement rate for depressed patients two weeks after being admitted to hospital is probably around 30 per cent)[65], unless his depression remits spontaneously a patient is not likely to remain cheerful for weeks on end on a dummy tablet. To suppose that a placebo can hold symptoms at bay indefinitely makes a nonsense of clinical psychiatry and reduces most of our methods of treatment and therapeutic ideas to a sort of mumbo jumbo. Few people would be prepared to treat an acute schizophrenic or a severely depressed patient with a placebo. The power attributed to the placebo, although needing to be considered in any drug trial, does seem to have been exaggerated.

However it is important, when assessing the activity of any drug, to recognise and attempt to distinguish specific from non-specific effects. Many patients undoubtedly improve simply from coming into hospital. In hospitals organised efficiently on therapeutic community lines, and particularly where there is a high staff–patient ratio, the specific effect of a drug will be relatively less noticeable because non-specific factors will be operating strongly, and vice versa. Hordern[92a] has suggested that this is one of the main reasons for controlled drug trials in understaffed American state mental

hospitals generally giving positive results, in contrast to well staffed university centres and psychodynamically orientated private hospitals where negative results from drug trials are more frequent.

The number of mental hospital patients has been steadily declining over the past twenty-five years both in the U.K. and the U.S.A.[29] There is disagreement over the reasons for this decline. It seems pointless to argue over whether this is due more to the influence of "therapeutic community" ideas and regimes or to the effects of psychotropic drugs and physical forms of treatment. Social and pharmacological factors must potentiate one another's effects. Tranquillisers will control disturbed behaviour, which in turn will lead to restrictions being further lessened.

In British mental hospitals the current trend is for the chronic patient to be returned to the community, and for the chronic hospital population to decline steadily. At the same time admissions and re-admission rates are rising[34]. Particularly in the London area, a high proportion of discharged schizophrenic patients relapse and require re-admission. More often than not this is due to inadequate follow up and after care and to patients stopping their drugs. However, other factors play a part such as the type of home to which a psychotic patient returns, and the way in which a patient is emotionally involved with his family[35,131,145,196].

DRUG TRIALS

In the past fifteen years, which represent roughly the modern drug era, each new drug introduced has tended to follow the same pattern; soaring enthusiasm, a plateau of acceptance for a time, followed by more realistic reassessment and, in many instances, a decline into oblivion.

After preliminary clinical experiments each new drug introduced is subjected to clinical trials. The object of a clinical trial is to determine whether a drug is effective and in what type of patient, how it compares with other forms of treatment, how it is to be given and in what dosage, and its side and toxic effects. Trials may be either uncontrolled or controlled.

(1) *Uncontrolled trials* are those when there are no untreated patients to compare with those receiving the drug. The results of these uncontrolled trials, which make up the majority of drug trials, are more likely to be optimistic than those of controlled trials. Without a base line provided by control groups the results of treatment with a new drug cannot easily be compared with the results of other treatments. However there is still a place for uncontrolled pilot trials based upon good clinical observation. In a subject like psychiatry, where signs of improvement are difficult to measure objectively,

carefully controlled trials are liable to miss important relationships.

(2) *Controlled trials* are those in which the progress of two or more groups of patients, treated identically except for each group receiving a different drug, is compared. Non-specific factors should play an equal role in each group, so that differences in outcome of the different groups should be due only to differences in specific effectiveness of the drugs being compared. A controlled trial may be *single blind*, the patients alone being unaware of what treatment they are receiving, or *double blind*, when the doctor carrying out the trial is also in the dark as to what drugs his patients are receiving, this fact only being known to a third party. Equivalent groups of patients should ideally always be obtained by *random selection*. A patient is selected to take part in a trial. Subsequently the group to which he is then allotted is decided purely by chance, by drawing lots from a hat or opening a sealed envelope or tossing a coin.

The purpose of the double blind trial is to exclude the influence of the doctor's personality on the outcome of treatment, and to remove as far as possible factors which are liable to bias him in his assessment of a drug's effects.

Provided similar groups of patients are selected in the *same way* as in the first trial, similar results should be obtained when a drug is repeated. But in practice several controlled trials of a drug may give contradictory results because patients used in the different trials are not similar.

Contradictory results may stem from other factors. The number of patients included in a trial may be inadequate. The trial period may be too short in view of the length of time the drug may take to act; for instance, two weeks' trial of an antidepressant drug is insufficient. The drug may not have been tested over a wide enough dosage range. And variables, such as side effects, may not be controlled or allowed for satisfactorily.

Hamilton[79,80] has pointed out that inferences drawn from a trial about the value of a drug apply only to *groups* of patients. How much can be inferred about an individual patient's response to that drug will depend upon how homogeneous the group under trial is for such factors as sex, age, diagnosis, constitution, length of illness, family history and so on. The more accurately the group is defined, the less its variability and the more accurately the reactions of individual patients to the drug can be anticipated. It is essential therefore to define and select as clearly as possible the type of patient to be included in a drug trial. Once selected each can then be allotted at random to a trial group. All too often unjustified general inferences and assumptions are made from the results of drug trials.

Certain characteristics of patients may influence both the therapeutic and side effects of a drug.

(*a*) *Sex*

The sexes may respond differentially to a drug. A female patient's responses may be affected by the stage of her menstrual cycle.

(*b*) *Age and maturity of a patient*

Children can take relatively large doses of barbiturates without adverse effects. Amphetamines, in dosages which may over-stimulate an adult, will sometimes lessen overactivity and quieten excitable hyperkinetic children. Phenothiazine derivatives are more likely to cause dystonic reactions in children and young adults than in older people. Antidepressant drugs do not generally help children or adolescent depressive states, nor depressed patients of inadequate or immature personality.

(*c*) *Personality and constitution*

Eysenck[62,63] has attempted to measure personality in psychological terms and to relate this to drug effects. He measures personality in terms of an extroversion–introversion continuum and links this with Pavlovian concepts of cortical inhibition and excitation. He has postulated that depressant drugs, such as the barbiturates, increase cortical inhibition and decrease cortical excitation, and thereby produce extroverted behaviour patterns. Stimulant drugs, such as amphetamine, decrease cortical inhibition, increase cortical excitation and thereby produce introverted behaviour patterns. From this theory, therefore, drug effects and the interaction between any drug and personality can be predicted. However, the basis upon which Eysenck's theory rests is not universally accepted.

Other effects

The importance of environmental factors has already been mentioned. Sympathetic and kindly treatment, intensive nursing, occupational therapy and social activities will influence the effects of drugs, even in chronic withdrawn schizophrenics.

The dosage of a drug may itself affect the outcome. A large dose of a drug may have the opposite effect to that of a small dose. For instance very small amounts of barbiturates will cause increased activity in some animals whereas large doses will result in sedation and reduced activity. Similarly a small dose of quinalbarbitone may stimulate a patient by reducing his tension, although a larger dose will cause him to feel drowsy.

Drug effects are also influenced to some degree by a patient's mood and expectations at the time when he takes the drug. Amphetamines or alcohol may make a man more depressed if he is depressed initially, or euphoric if he is in a happy state of mind.

POLYPHARMACY

Mixtures of drugs may have antagonistic, synergistic, or additive effects. For instance barbiturates sedate and amphetamines stimulate but in combination the advantages of these two drugs appear to be reinforced whilst their side effects are antagonised. On the other hand side effects are potentiated to dangerous levels by combining morphine or pethidine with a monoamine oxidase inhibitor (MAO inhibitor). Various combinations of drugs are marketed together now. Although this is helpful when dealing with patients who object to taking several tablets at a time, it is undesirable in that dosages of different drugs need to be varied from patient to patient and not prescribed in a "fixed" proportion.

Since the basic causes of most psychiatric diseases are unknown, treatment usually needs to be symptomatic. It is inevitable therefore that two or more drugs may sometimes have to be given concomitantly. An antidepressant drug such as imipramine or phenelzine may improve depressive mood but fail to alleviate agitation or anxiety without the aid of a tranquillising drug. Schizophrenic symptoms will respond to a phenothiazine derivative but depression and anergia may remain and delay full recovery unless an antidepressant drug is also given. Similarly it may be necessary to combine drugs with such physical treatments as ECT or modified insulin. Psychotherapy and moral support, particularly in treating neurotic conditions, will usually be needed in addition to drugs if maximum improvement is to occur.

The type and severity of psychiatric illness will influence to some extent the treatment given. A schizophrenic illness or severe depression, especially if suicide is a possibility, will usually result in the patient being admitted to hospital. On the other hand the majority of patients with neurotic disorders or mild depressive states can be treated satisfactorily as out-patients by means of drugs and psychotherapy, supplemented by ECT if necessary.

Most psychiatric illnesses are probably brought about by several factors. There are constitutional weaknesses within the patient, the result of inherited predispositions and earlier conditioning factors. There are stresses acting upon the patient, from outside and inside. All or any of these factors may interact and combine to bring about psychiatric symptoms and illness.

In order to use drugs effectively it is necessary not only to make an accurate diagnosis of the patient, but to obtain as full an idea as possible of all the possible factors, physical and psychological, internal and external, past and present, which may have contributed to the condition.

In general, psychotropic drugs are of greatest importance in the

treatment of serious mental diseases. They are less, but still important, in the treatment of minor or neurotic mental illnesses, in which emotional problems and conflicts usually play a greater and more obvious role and where psychotherapy is particularly helpful.

AIMS OF TREATMENT

Treatment may aim to be curative or suppressive.

(1) *Curative treatment.* Most "cures" are, in fact, spontaneous recoveries, although these may have been helped by drugs. Only such diseases as general paralysis of the insane (GPI), pellagra or myxoedema are *curable* by means of drugs, although in (*b*) below the drugs may be looked upon as contributing to a cure. In general psychotropic drugs suppress and control symptoms, they do not cure the illness.

(2) *Suppressive treatment.* (*a*) In the majority of psychiatric illnesses symptoms are merely suppressed by drugs. Many psychiatric illnesses, particularly affective disorders, are self remitting. In such cases drugs will have to be continued until spontaneous recovery occurs, and if the drugs are stopped too soon symptoms will return. In chronic mental illness such as schizophrenia, where remission is unlikely, drugs will have to be continued indefinitely.

(*b*) In some cases drugs, by suppressing symptoms and damping down tensions, can break a vicious circle and help a patient to regain sufficient confidence and drive for him to resolve the problems and conflicts which lie behind his symptoms.

(*c*) In those "inadequate personalities" who react in an excessive and prolonged manner to relatively minor stresses, drugs given in the early stages can prevent anxiety and depression building up to serious proportions.

(*d*) Recurrent depressive illnesses may sometimes be prevented by giving the patient a maintenance dose of the appropriate drug. When a recurrence can be anticipated, as in some manic depressive states, a drug can be started a few weeks beforehand in the hope of aborting the attack.

SIDE EFFECTS AND TOXIC EFFECTS OF DRUGS

Side effects differ from toxic effects. The side effects of a drug are related to its pharmacological activities. They are liable to occur to some extent in all patients taking that drug, and depend on constitutional differences, dosage and what other substances may be present. They decrease and disappear when the drug is reduced in dosage or stopped.

Toxic effects on the other hand are uncommon, and are probably the result of a hypersensitivity reaction on the part of the patient to the drug. They are not related to dosage and they may develop at any time, although commonly within the first four to six weeks of starting treatment, as for instance jaundice from chlorpromazine or a hydrazine MAO inhibitor, or the rare case of agranulocytosis with imipramine.

It is essential for a physician to know what side and toxic effects may result from a drug he may wish to prescribe. Not only should a patient be forewarned about possible side effects but his doctor must be able to weigh all the possible risks against the probable advantages to the patient of treatment with the drug. It is no more right to prescribe a potentially lethal drug for some relatively minor state of distress than it is to refuse ever to consider the use of a drug, or combination of drugs, on the grounds that such treatment is dangerous. The morbidity and mortality of psychiatric illnesses should never be overlooked.

In the U.K. a Committee on Safety of Drugs was formed in 1964. There are three subcommittees to this, dealing with toxicity, clinical trials and adverse reactions. An early warning system now exists to inform doctors and others concerned of suspected adverse reactions to drugs.

PHARMACOGENETICS

Efforts to distinguish and describe clinically different types of depression have not met with agreement.

Yet it has become increasingly apparent that certain types of depression will respond to one type of treatment and not to another. This is particularly so since the introduction of the antidepressant drugs. For instance, a patient will respond fully when treated with an antidepressant drug of the MAO inhibitor group, and not at all to imipramine or another of the tricyclic antidepressant group. What is more, when a patient responds fully to an antidepressant drug he will generally continue to respond to another drug *of the same group*, not only during that depression but also later if there should be recurrences. Evidence has also been gathered to show that first degree relatives who become depressed will generally all respond to drugs of the same antidepressant group and not to the other[6].

These findings have led to the suggestion that there are fundamental biochemical abnormalities underlying depressive illnesses, and it is these which determine whether a patient responds to one or other antidepressant group of drugs. Pare[142] suggests that most patients with depressive illness may have a genetic predisposition,

greater in some, less in others, which will determine the type of biochemical abnormality precipitated by exogenous stresses. Endogenous depression will require less, reactive depression more stress.

CLASSIFICATION OF PSYCHIATRIC DRUGS

The classification and terminology of drugs used in psychiatry is almost as confusing as that used for psychiatric disorders.

Tranquillisers or ataractics differ by definition from *sedatives and hypnotics* in that they alleviate anxiety without causing patients to become so drowsy.

Antidepressant drugs like imipramine and the monoamine oxidase inhibitors differ from euphoriant drugs such as amphetamine in that they appear to act specifically against depressive symptoms.

Tranquillisers and antidepressant drugs are usually included together in the vague but widely used descriptive term *psychotropic drugs*.

In order to avoid further confusion a simple classification is used below:

Class of drug	Examples
A. Stimulant drugs	
1. Euphoriants	Amphetamine
2. Antidepressants	(*a*) Imipramine (Tofranil) (*b*) Monoamine oxidase inhibitors, such as phenelzine (Nardil)
B. Depressant Drugs	
1. Tranquillisers affecting the extrapyramidal system (Neuroleptics)	(*a*) Phenothiazine derivatives (*b*) Reserpine and benzoquinolizine derivatives (*c*) Butyrophenone derivatives such as haloperidol (Serenace)
2. Tranquillisers without extrapyramidal effects	(*a*) Phenothiazine derivatives such as promazine (Sparine), promethazine (Phenergan) (*b*) Lithium salts (*c*) Diazepines, such as chlordiazepoxide (Librium) (*d*) Meprobamate (Equanil) (*e*) Others such as benactyzine (Suavitil), hydroxyzine (Atarax)
3. Sedatives and hypnotics	(*a*) Barbiturates (*b*) Nonbarbiturates such as glutethimide (Doriden), nitrazepam (Mogadon), chloral hydrate, paraldehyde

Class of drug	Examples
C. Hallucinogenic (Psychomimetic or psychodysleptic drugs)	Lysergic acid diethylamide (LSD)
D. Vitamins and Hormones	
E. Miscellaneous	(*a*) Disulphiram (Antabuse) (*b*) Apomorphine

CHAPTER II

STIMULANT DRUGS

CLASSIFICATION OF DEPRESSIVE ILLNESS

The term *depression*, perhaps more than other psychiatric terms, is open to misunderstanding since it is used in so many different ways.

The traditional division of depression into two broad categories, reactive and endogenous, is contested by those who believe that attempts to distinguish one type of depression from another are fruitless, and regard all depressive illnesses as qualitatively the same, only differing in quantity one from another. Adolph Meyer, Mapother and Aubrey Lewis[117] have argued and claimed to show that endogenous and reactive depressions cannot be distinguished from one another. Nevertheless other psychiatrists[102,130] have continued to maintain that at least two types of depression exist and can be distinguished from one another.

The basic causes of depressive illness are still unknown but effective treatment in the form of electroconvulsive therapy has been available for over twenty-five years, and antidepressant drugs for nearly ten years. There is evidence that not all types of depression will respond to ECT, but rather only those with symptoms suggestive of endogenous depression[3]. There is also evidence that the two main groups of antidepressant drugs are effective in different types of depression. Patients with symptoms of endogenous depression tend to respond better to imipramine or to one of its tricyclic analogues. Imipramine is less effective in the treatment of patients with symptoms of reactive depression; these generally respond better to treatment with a monoamine oxidase inhibitor[167].

A valid classification is unlikely to be arrived at from the results of treatment alone, nor is it likely that the results of treatment may be predicted with absolute certainty on the strength of a psychiatric diagnosis alone. But it is important that efforts to differentiate categories of depressive illnesses should continue if only because of the increasing importance of predicting the results of treatment with different drugs. In the following section depressive illness has been divided into two main groups:

(*a*) *Reactive depression*, roughly equivalent to what is sometimes called neurotic or psychogenic depression and

(*b*) *Endogenous depression*, which includes conditions such as manic depressive psychosis and involutional melancholia.

Table 1 sets out the main clinical differences between these two types of depression.

TABLE I

Reactive and endogenous depressions
Clinical differences

	Reactive Depression	*Endogenous Depression*
Sleep	Difficulty in getting to sleep and/or broken sleep. But tired and ready to sleep in the morning	Waking early after only a few hours of sleep. *May* also be difficulty in getting to sleep
Diurnal variation of mood	Symptoms increase as day lengthens Worse in evenings	Worse on waking and in early morning Improves towards evening
Self blame and guilt	Absent. Tend to blame others	Present
Weight loss	Not marked. Rarely more than 7 lb	May be severe. Frequently more than 7 lb
Retardation	Never present, although patient may be "muddled"	May be present
Autonomic symptoms	Tachycardia, Palpitations, Diarrhoea } But may also be present in endogenous	Sweating, particularly at night Constipation
Body Build	Athletic (mesomorphic) and asthenic (ectomorphic)	Pyknic (endomorphic)
	Of less significance	
Family history of manic depression or recurrent depression	Absent	Present
Age of onset	Usually below 40	Any age, but often above 40
Reactive factors	Marked	Often slight

From the point of view of response to treatment, it is important to assess whether a patient has an "adequate" or "inadequate" basic personality. The concept is a vague one, implying:

(*a*) Freedom from previous *neurotic* breakdowns.
(*b*) A good work record and therefore reasonable powers of persistence.
(*c*) Freedom from serious social maladjustments and undesirable habits such as alcoholism.

A patient with an "inadequate" personality is prone to develop depressive symptoms under relatively minor stress. His response to treatment with psychotropic drugs, as with ECT, is variable and not generally impressive. The "adequate" personality's response to treatment is much more consistent and predictably satisfactory.

(1) EUPHORIANT DRUGS

(*a*) *Amphetamine*

Amphetamine was introduced into clinical practice in 1935, at first for the treatment of narcolepsy. The drug's stimulating effect on the central nervous system and the transitory euphoria induced led to its use in the treatment of depressive illness.

A mood of depression, if not too severe, is sometimes quickly relieved when the drug is first taken. But these effects last a few hours only and are often succeeded by increased feelings of depression or agitation. In addition, tolerance to the drug rapidly builds up until, after about ten days, in spite of increasing dosage, the drug ceases to have much therapeutic effect.

Amphetamines therefore have almost no place on their own in the treatment of serious depressive illness. Controlled trials comparing dextroamphetamine with placebo in the treatment of endogenous depressive illness have found the amphetamine to be no better than the placebo. However some inadequate personalities, unable to cope effectually with every day tensions, mildly and chronically depressed and constantly complaining of lethargy and apathy, do seem to respond to amphetamine or to its optical isomer dextroamphetamine, particularly when this is combined with a sedative such as amylobarbitone (Drinamyl), or a tranquilliser. These patients not infrequently become dependent upon a relatively small daily dosage, between 5–20 mg a day.

Miss E., 46, a Civil Servant, was first seen about three months after the death of the head of her department. She had been his personal assistant for ten years, and had made herself indispensable to him. She

lived with her mother and had not married because she felt her mother needed her.

She described herself as a somewhat tense and highly strung personality, inclined to worry excessively over trifles, very conscientious, a pillar of the local church, always happy providing she could be helping others, but with few close friends. Since her boss's death she had felt anxious, apprehensive about the future, had lost interest in her work, felt tired and irritable and that her life was without purpose. She had difficulty in getting to sleep but once asleep, slept heavily. Her weight was steady and she continued to work. All her symptoms increased after her mother became ill and died six months later.

She was treated with phenelzine at first, combined with various tranquillisers. Subsequently she was given tranylcypromine, imipramine and amitriptyline in turn, none of which produced much improvement. Psychotherapy showed up the immaturity of her personality and her dependence upon others. Eventually she was admitted to hospital and given 4 ECT combined with semi-continuous narcosis. This improved her mood and lessened her anxiety temporarily, although she subsequently worried about what she called her "memory upset". But after some weeks the old symptoms began to return. She was then given Drinamyl (10 mg d-amphetamine a day) and reported feeling much calmer. She has remained on this dosage for three years, being seen every 4–6 weeks for supportive psychotherapy. Whenever attempts to stop the drug are made she complains of an immediate return of symptoms. She has never felt any need to increase the dosage beyond 10 mg a day.

A small number of patients become addicted in the sense of requiring very large and increasing amounts of amphetamine sometimes in excess of 50 mg a day.

M., aged 32, the son of a wealthy self-made man, went into his father's business when he left school at 16. He claimed that he had helped to expand the business, but when his father died five years later he soon found himself in debt and unable to carry on.

His personality was "inadequate". Throughout his school life and business life he was never able to deal realistically and adequately with stressful situations but sheltered behind over-indulgent parents. After his father's death he collapsed into a state of chronic depression which was unrelieved by ECT. Tranylcypromine, of all the antidepressant drugs, for a time gave him confidence and energy but this improvement was not sustained. Dextroamphetamine, on the other hand, gave him an immediate boost and on this drug he felt better than he had done for years. However in order to maintain the effect he had to increase the dosage progressively until eventually he was taking 25 tablets (125 mg) of dextroamphetamine a day. In order to counteract the insomnia, restlessness and autonomic effects of this dosage he began to take in addition increasing amounts of barbiturates.

Numerous unsuccessful attempts to wean him off these drugs have been made but he remains addicted.

Dextroamphetamine and Drinamyl are sometimes useful in the

treatment of pre-menstrual tension. 5 mg once or twice a day, in some cases combined with a diuretic or mild analgesic, can be given for a week or ten days before menstruation. There is a significant relationship between pre-menstrual symptoms and neuroticism[40], but the relationship is not a simple one and it is not easy to predict when dextroamphetamine will help. In any case the pre-menstrual syndrome occurs in about a quarter of all women, but only the more severely affected will require treatment.

Children tolerate amphetamine well. The drug may be particularly useful in children with behaviour problems associated with abnormal brain waves. Treatment with dextroamphetamine may result in both behaviour and the electroencephalographic recording becoming more normal. The type of child who is likely to respond well is hyperkinetic, irritable and prone to temper tantrums.

Dextroamphetamine is also helpful in the treatment of the child with nocturnal enuresis who sleeps deeply. 10 mg given when he goes to bed may lessen the depth of sleep sufficiently for him to awaken in response to the fullness of his bladder before micturition occurs.

Amphetamines may be safely combined with other drugs, although some caution is needed with monoamine oxidase inhibitors. They are useful in counteracting the soporific effects and anergia which may result from large doses of phenothiazine derivatives given to schizophrenics, or the initial muzziness and sleepiness which imipramine and amitriptyline may produce during the first few days of treatment. Amphetamines are also used to counteract the sedative effects of anticonvulsant drugs in epileptic patients. A combination of amphetamine and epanutin will sometimes control and prevent outbursts of disturbed behaviour in patients who, without openly displaying epilepsy, nevertheless have "epileptoid" brain wave recordings.

SIDE EFFECTS

The side effects of amphetamine reflect sympathetic overactivity; dryness of mouth, sweating, tremor, tachycardia, hyperreflexia, insomnia, diminution of appetite and bowel changes. Some patients are unable to tolerate the unpleasantness of these effects, even when they are reduced by the addition of amylobarbitone (Drinamyl). Dextroamphetamine tends to cause less side effects than amphetamine itself and is therefore to be preferred.

Restlessness and anxiety may increase markedly, which may be dangerous in a patient already agitated or suicidal, and schizophrenic symptoms may be exacerbated. Rarely, when combined with a MAO inhibitor, particularly tranylcypromine, a hypertensive crisis is precipitated. This will only occur if the amine oxidase is totally inhibited and the catecholamine stores are already saturated.

Warnings about the dangers of giving amphetamine with a MAO inhibitor have been issued, but such reactions are excessively rare when amphetamine is given by mouth. The real danger arises when amphetamine is given intravenously.

Psychopathic personalities may have tensions increased by amphetamine to a level at which they begin to "act out", to behave aggressively and destructively. On the other hand some aggressive psychopaths become less aggressive when given amphetamine, sometimes combined with epanutin.

Chronic addiction is associated with irritability, restlessness, insomnia and loss of weight. Not infrequently the addicted individual combines dextroamphetamine with sedatives or alcohol in excessive amounts.

A clinical state resembling paranoid schizophrenia may occur during the course of amphetamine addiction[16], or following the ingestion of a dose in excess of 50 mg. Anxiety, restlessness, ideas of reference and paranoid delusions develop. Visual and auditory hallucinations sometimes occur, *in a setting of clear consciousness*, unless barbiturates, tranquillisers or alcohol have also been taken in large amounts. However, thought disorder does not occur, although a patients' excited talk and euphoric flight of ideas may sometimes give a false impression of this.

Generally the symptoms of amphetamine psychosis resolve completely within about ten days of stopping the drug, and the drug can be fully withdrawn at once without any effects. Occasionally amphetamine intoxication may precipitate a schizophrenic illness in a predisposed individual which will then run its own course.

Treatment of amphetamine addiction or psychosis nearly always requires admission to hospital. The drug can be stopped at once without fear of withdrawal symptoms. Heavy sedation or, in severe cases, continuous narcosis, is usually advisable for the first week or fortnight, but care should be taken not to allow the patient to become dependent on barbiturates or tranquillisers. Weight and nutrition should be restored before the patient is discharged.

(*b*) *Methylamphetamine* (*Methedrine*)

Methylamphetamine is similar but milder in its therapeutic and side effects to dextroamphetamine when given by mouth. It is a methyl derivative of the racemic mixture, dextro and laevo amphetamine.

Its chief value lies in the fact that it is soluble and so can be injected intravenously. When given intravenously its effect is to lessen the patient's inhibitions and cause him to "abreact", to relieve pent-up emotions associated with some past traumatic and sometimes suppressed experience. It is also useful as an aid in treatment

by conditioning and deconditioning methods, not only by helping to increase a patient's conditionability but also by making him more suggestible. Methylamphetamine may also be combined with lysergic acid, when it will heighten and prolong the effects of that drug. It may be given intravenously at the same time as lysergic acid is ingested, or at any time during treatment in order to exploit some particular emotion or reaction of the patient (see page 124).

Methylamphetamine is also helpful in the treatment of allergic skin disorders, such as eczema[47,178a]. A high proportion of such patients show marked obsessional traits, are over-anxious, outwardly timid and unable to express easily and openly their resentments and more aggressive emotions. Suppressed resentments frequently precede eczema or urticarial reactions. These patients often feel compelled to scratch themselves, driven to do this as much by their tensions as by pruritus. Particularly in this type of patient, intravenous methylamphetamine will help to release pent-up feelings, with relief of tension and improvement of skin.

DOSAGE AND SIDE EFFECTS

The dose of methylamphetamine is 5–10 mg by mouth; it is not advisable to exceed 20 mg a day. The intravenous dosage is 10–30 mg.

Care is needed over giving methylamphetamine intravenously. The ideal patient for this treatment has an obsessional tense personality, is aged between 20–40, and has difficulty in openly expressing his deeper feelings, particularly if these are aggressive.

Hypertension is a contra-indication and it is also advisable not to give methylamphetamine to patients over 45 years of age; their reactions are less predictable and agitation may be the result. Schizophrenia, paranoid states and psychopathy are contra-indications, although a small dose of methylamphetamine may help diagnostically in an obscure case of schizophrenia by bringing out bizarre ideas or delusions. Patients with an obsessional personality become relaxed, but wide awake and alert after injection. In contrast, hysterical personalities sometimes react in the opposite way and fall asleep. Patients with endogenous depressive states should never be given the drug; not only is the mood of depression merely lifted temporarily or not at all but there is a danger that agitation and the risk of suicide may be increased. Methylamphetamine must never be injected if the patient is taking, or has had within the previous two weeks, a monoamine oxidase inhibitor. If this occurs a dangerous hypertensive crisis is likely (see page 37).

(*c*) *Other euphoriant drugs*

There are several compounds with weaker but similar actions and side effects to the amphetamines.

Methyl-phenidate (Ritalin). This drug can be given orally, 10–40

mg a day, or intravenously (20 mg). Its uses and contra-indications are similar to those of the amphetamines.

Phenmetrazine (Preludin). Phenmetrazine is used mainly for its anorexic effects in the treatment of obesity, but a substantial number of these patients are depressed, inadequate personalities who easily become addicted to this drug. The dose is 25 mg once or twice a day.

Pipradol (Meratran). This drug is rarely used now in this country. The dose is 1–7·5 mg by mouth.

(2) THE ANTIDEPRESSANT DRUGS

Monoamine oxidase inhibitors (MAOI)

Until 1957 the amphetamines and related compounds were the only drugs available for treating depression. But they are general euphoriants without *specific* antidepressant properties and their usefulness in depressive illnesses is extremely limited.

In 1957 a major advance in the treatment of depressive illness occurred with the introduction of iproniazid (Marsilid) and imipramine (Tofranil) into psychiatry.

Iproniazid, a hydrazine derivative of isonicotinic acid, was first used in the treatment of tuberculosis during a search for a successor to isoniazid. It proved too toxic in its effects to succeed isoniazid, but its remarkable antidepressant effects and the way in which it increased appetite were noticed. Subsequent investigations by Kline[106] and his co-workers, after a number of unsuccessful trials on schizophrenics, confirmed its value as an antidepressant and led to its introduction into psychiatry.

In contrast to isoniazid, iproniazid was shown to have a strong inhibitory effect upon the enzyme monoamine oxidase (MAO). MAO is concerned in the breakdown of monoamines such as 5-hydroxytryptamine (5 HT), noradrenaline, tryptamine and tyramine, all of which are thought to be concerned with normal brain metabolism. (For an account of their metabolism, see appendix II.) But not all the pharmacological effects of MAO inhibitors are due to this latter property. The MAO inhibitors also reduce the activity of other enzymes and this probably accounts for individual differences between individual drugs.

Iproniazid proved to have toxic effects, particularly on the liver, and as a result the drug was withdrawn from use in the U.S.A. and used cautiously in the U.K. for several years. Since then compounds analogous to iproniazid have been introduced clinically, all having in common the ability to inhibit MAO. These are mainly hydrazine type MAO inhibitors, such as isocarboxazide (Marplan), phenelzine (Nardil), nialamide (Niamid), phenoxypropazine (Drazine), and

mebanazine (Actomol). Two non-hydrazine MAO inhibitors are available for clinical use, tranylcypromine (Parnate) and pargyline-hydrochloride (Eutonyl). Of these only tranylcypromine is an effective antidepressant.

All the MAO inhibitors are of the "hit and run" type; that is, although they are themselves excreted promptly, their effects at an enzymatic level continue for a week or more after their discontinuation. This sometimes poses problems when other drugs may be required to be given.

CLINICAL EFFECTS

It is generally agreed that the MAO inhibitors are most effective in reactive depressive illnesses, particularly those in which phobic and hysterical symptoms are prominent [194]. This type of depressive illness used to be particularly difficult to treat. ECT often did more harm than good and sedative or tranquillising drugs, while relieving tensions, more often than not left the patient still feeling depressed and lacking in energy and drive.

Reactive depressions may present in a variety of ways, depending upon how much accompanying tension there is and the basic personality structure of the patient.

The patient may complain of loss of confidence in himself, in his ability to work efficiently or to mix easily with other people. There may be a constant irrational sense of apprehension, an inexplicable fear that some personal disaster is about to occur. Sometimes this excessive anxiety is displaced on to innocuous objects or situations. The patient may become terrified of and unable to travel, afraid to go into a shop, or even to venture out of doors at all. Other patients become afraid of being left alone and demand that a close relative or someone reliable stays constantly with them. Such patients usually have a dread that they may lose control and disgrace themselves in public, go off their heads or do some terrible harm. Hysterical features and regressive behaviour not infrequently intrude and complicate the picture.

Somatic symptoms such as headache, muscle pains particularly over the precordium, breathlessness, palpitations, diarrhoea, dizziness and other signs of autonomic imbalance may dominate the clinical picture. A patient with such symptoms becomes convinced that he has a fatal disease and fails to be reassured in spite of thorough and repeated investigations.

Concentration is impaired and the patient feels at times as though his head were packed with cotton wool; he cannot think clearly nor attend to what is happening around him, and he comes to believe that he is losing his memory or going mad. He is irritable, particularly to those with whom he is close. Sleep disturbance is a common symptom and usually takes the form of difficulty in getting to sleep.

Once asleep the patient may sleep heavily, waking up in the morning feeling tired and unrefreshed. Or he may waken frequently throughout the night, dreaming vividly and unpleasantly, and only fall into a deep sleep when it is time to get up. Occasionally the patient gets off easily and wakens in the early hours of the morning, feeling ghastly and unable to sleep again, but this is more typical of endogenous than reactive depression. Tiredness and lack of energy are common complaints and patients may fall asleep as soon as they sit down or relax. But generally such patients are unable to relax and feel at their worst when they have nothing on which to concentrate. Appetite is usually diminished and there may be some weight loss but this is never so severe as in an endogenous depression and is usually less than 7 lb. Sometimes appetite is increased and the depressed patient will put on weight, or he may develop cravings for certain types of foods. Sexual appetite is also usually diminished or lost, although as with food a patient may occasionally have increased sexual cravings during the illness.

Self-blame and feelings of guilt about past behaviour are unusual. Rather, the patient with reactive depression tends to blame other people for his troubles. Insight is never completely lost as it may be in endogenous depression, although a mood of pessimism and hopelessness may colour his thoughts and impair his judgement. The latter half of the day is when symptoms are usually at their worst; some patients may feel almost normal for a few hours after getting out of bed. An almost constant feature of women patients is the exacerbation of symptoms which occurs a week or so before menstruation.

Symptoms may have been constantly present for years, or may have run a phasic course without ever completely remitting. Secondary fears and complications tend to develop and to become as disabling or even worse than the primary symptoms. Alcoholism may develop in predisposed patients, although many patients with reactive depression are liable to feel worse if they take alcoholic drinks and to experience palpitations, flushing, or dizziness. Smoking often increases.

In other individuals symptoms develop rapidly after some special or prolonged stress, or develop slowly but progressively after childbirth, a debilitating illness, or treatment with a depressant drug such as reserpine or methyldopa (Aldomet). The clinical picture is sometimes very much akin to *anxiety hysteria*, particularly when phobic symptoms are in the fore front, or when tiredness and lack of energy are the main complaints to what in the past used to be called *neurasthenia*.

Mrs. G., aged 34, had been unable to leave her house for two years, even when accompanied by her husband, for fear of developing attacks of panic. Her first anxiety attack occurred when she was 18, while on

her way to a party shortly after announcing her engagement. She felt faint, dizzy and sweaty, her heart pounded, there was a sense of constriction across her chest and she had difficulty in breathing. These symptoms lasted acutely for about thirty minutes, but she remained tense and afraid of a repetition for the rest of the day. There were recurrences on and off over the next eighteen months, usually brought on by the prospect of having to meet groups of people, but never so severe as the initial attack. After marriage, when she moved away from her parents' home, she improved steadily and slowly lost her anticipatory fear of further panics.

She was well throughout her first pregnancy and there were no post-natal relapses. But a year later she miscarried at three months, quickly became pregnant again, and gave birth to a child with a severe congenital heart condition which died at four months. She became very depressed and phobic anxiety recurred. This lasted for a year until she again became pregnant. During this pregnancy she felt well and all symptoms lifted. But phobic anxiety recurred as soon as the child was born and lasted until her fifth (unwanted) pregnancy two years later. After this child was born five years ago her anxiety and depression became much worse and she was virtually "housebound" for the two years before being seen. She had had six months intensive psychotherapy, and been given various tranquillisers and sedatives, without any lasting benefit.

Her mother was a dominating woman who had constantly "used" her daughter to compensate for the deficiencies she felt to exist in her own marriage and life situation. Mrs. G. was a perfectionist, never able to express openly her resentments and anger, and she had clearly broken away completely from her mother's domination and influence. Her husband was a quiet, somewhat inhibited and emotionally cold chartered accountant.

Mrs. G. was well aware of her frustrations and pent-up resentments, particularly towards her mother and husband, and the part that they played in causing her symptoms. But she remained severely disabled by her "fear of the fear".

Basically her personality was adequate. She was given phenelzine 15 mg and chlordiazepoxide 10 mg, both three times a day, and quinalbarbitone 45 mg to take if and when she felt panicky. After three weeks she felt calmer and more confident. She was encouraged to go out, at first with friends and then alone, increasingly long distances. Undesirable habit patterns were thus slowly but steadily broken. She had to remain on the full dose of phenelzine and chlordiazepoxide for six months, and required one to two tablets a day of each drug for a further year. But at the end of this time she was symptom free and able to stop all drugs.

J.M. is 38. He gave a four year history of feeling so tired that at times he found it impossible to stay awake. This occurred both at work and at home, and sometimes while driving. At night he slept heavily and soundly, but woke up feeling unrefreshed. He was moody and unsociable, his concentration was impaired and he felt irritable, lacking

in confidence and without zest for living. His libido was diminished, but he had no loss of appetite or weight.

He was a reserved, quiet, introspective man who rarely allowed his deeper feelings to show. In the past he had been given drinamyl, with some temporary benefit, amitriptyline which had made him feel much worse, and numerous tranquillisers. He was given tranylcypromine 20 mg in the morning and 10 mg at noon, for three months, which produced some improvement, and then phenelzine, 15 mg three times a day. On phenelzine all symptoms of tiredness and tension disappeared and he felt "normal". He has needed to remain on this drug, varying the dose and at times stopping altogether for several months, for the past four years.

Although these patients when ill may give the appearance of being inadequate or neurotic personalities, *the MAO inhibitor responder is not basically inadequate*. Typically he is a somewhat over-conscientious, sensitive, highly strung personality, often with an aggressive driving façade which hides an underlying sense of inferiority and dependency. He may be a highly successful businessman, breaking down in his late 30's or early 40's only after a great deal of worry and stress, such as for instance dealing with a take-over bid. Frequently his tension and depression are reactions to emotional strains which have been present and growing for years. Such a person pushes himself to the limit of his capacity and, in spite of increasingly disabling symptoms, attempts to carry on with his work and responsibilities.

Lifelong inadequate personalities with somewhat similar symptoms are not generally helped by the MAO inhibitors. In fact such patients may become more tense and in some cases inhibitions may be lessened, releasing irresponsible or anti-social behaviour. Generally they respond better to barbiturates, tranquillisers, or drinamyl, but there is a serious risk of addiction in this type of patient and it emphasises the importance of differentiating the pre-morbid personality. A patient who has since childhood constantly given up or broken down on encountering relatively minor difficulties is not likely to improve on one of the MAO inhibitors.

CLINICAL TRIALS

Numerous trials of MAO inhibitors have been reported, the majority of which have been uncontrolled. Kline[107] stated that 75 per cent of cases of depression responded to iproniazid and claimed that the drug was as good as, or better than, ECT. Subsequent trials, such as the controlled ones by Rees and Benaim[158] and Kiloh[103] on depressed hospital in-patients, produced less impressive rates of improvement, although the drug was certainly superior to a placebo.

Most of the more reliable reports emphasise that patients with

severe depressive states do not benefit from treatment with MAO inhibitors and that the results of ECT are much superior[129]. Kiloh, for instance, found that treatment with iproniazid resulted in 54 per cent of the trial group responding, compared to 89 per cent with ECT. However, the relapse rate after ECT is quite high, and six months after treatment he found the response rate from the two treatments to be comparable, 48 per cent after ECT compared to 40 per cent with iproniazid. Kiloh and others have emphasised the need to continue treatment with iproniazid and other MAO inhibitors for a year or more if necessary, in order to avoid relapse. It is apparent that the conflicting results of controlled trials with antidepressant drugs are largely due to the use of dissimilar patient material.

Many investigators have reported that MAO inhibitors give better results in cases of reactive or "atypical" depression. West and Dally[194] reported a high rate of success with iproniazid in reactive depressions, particularly when complicated by hysterical and phobic symptoms. Kline found iproniazid to be particularly useful in lifting depressive tiredness and anergia. And later, Sargant and Dally[168] reported the effectiveness of combined treatment with a MAO inhibitor and a tranquilliser in phobic anxiety states occurring in patients of adequate pre-morbid personality.

Medical Research Council investigators[129] who carried out a trial* of treatments of depressive illness (1965) reported that phenelzine was no better than a placebo, in contrast to the efficacy of ECT and imipramine. These negative findings are probably due to the fact that patients admitted to the trial all had symptoms suggestive of endogenous depression[128].

Comparison of the results of treatment with MAO inhibitors and imipramine and its analogues are misleading because the two groups of drugs are each most effective when acting on different types of depressive illness.

The action of MAO inhibitors is to reduce excessive tension, lift the mood of depression, and restore the patient's sense of energy and confidence in himself. The autonomic system becomes more stable and ceases to react so excessively to strains. Appetite improves (unlike the effect of amphetamine) and weight may be gained. Phobic anxiety lessens and conditioned avoidance reactions in turn begin to weaken. Disturbances of sleep and sexual feelings may not improve as quickly as other symptoms, although this is sometimes due to these symptoms being side effects of the MAO inhibitors.

These improvements do not occur immediately after starting the MAO inhibitor. There is always a *time lag* of several days after

* Medical Research Council trial characteristics: All patients were between 40 and 69 years; their depressed mood was accompanied by such symptoms as self depreciation with a morbid sense, sleep disturbance, hypochondriasis, retardation of thought and action, agitated behaviour.

starting the drug but evidence of response, if it is going to occur, should be apparent within fourteen days of beginning treatment. In most patients signs of response appear after 5–10 days. Soon after starting treatment and before the therapeutic response occurs, some patients feel sleepy and have difficulty in thinking clearly. These side effects, which have been attributed to a rise in concentration of 5 HT which precedes that of noradrenaline, generally last for only a few days.

Combined treatment with tranquilliser

When *anxiety* is a prominent symptom the effects of a MAO inhibitor may be considerably enhanced by combining it with a sedative or tranquillising drug. A minor tranquilliser such as chlordiazepoxide (Librium) or nealbarbitone (Censedal) combined with a MAO inhibitor is particularly effective when *phobic anxiety* predominates. A small dose of one of the piperazine phenothiazine derivatives, such as perphenazine (Fentazin), is sometimes better when anxiety is more diffuse and "free floating".

Patients with *cardiac neurosis* or *effort syndrome*, unresponsive to reassurance or treatment with sedatives or tranquillisers alone, do particularly well with this combination of drugs. Tachycardia, extra systoles, breathlessness, and pain over the heart may convince the patient that he has heart disease and lead to a vicious spiral of mounting anxiety and autonomic over-activity.

R., at 38, had built up a business empire. His only interest lay in his work. He worked sixteen hours a day, seven days a week, without relaxation. Underneath his driving successful façade was a sense of insecurity and a constant fear of failure.

One day during a business meeting, he suddenly experienced a gripping pain over his heart and palpitations. He felt faint and became terrified that he was about to die. Repeated examination and electrocardiographic recordings gave no sign of coronary artery disease, but R. would not be convinced. For over a year he led the life of an invalid, cut down or gave up most of his business activities, and lived in constant fear of another and final heart attack.

Eventually he agreed to seek psychiatric advice. He was given iproniazid 50 mg and chlordiazepoxide 10 mg three times a day. Within two weeks there was a dramatic improvement and after six weeks he was restored to his former energetic self.

Even when true angina is present anxiety may increase symptoms out of all proportions. For instance a doctor's wife suffering from angina became increasingly agitated and was eventually unable to walk across a room without developing anginal pain. Treatment with phenelzine 15 mg and chlordiazepoxide 5 mg, both three times a day, improved her to such an extent that within three weeks she was able to walk a quarter of a mile to the shops without difficulty.

There is no evidence however that the MAO inhibitors will relieve anginal pain by increasing coronary blood flow.

Good results may follow treatment with a MAO inhibitor combined with a tranquilliser of patients with obsessional or compulsive symptoms when these are the result of or are exacerbated by underlying depression. But although these combinations of drugs will lift depression and cause obsessional tensions to lessen or disappear, they will not help pure obsessional states. These remain generally unresponsive to all treatments (apart perhaps from modified leucotomy).

Mrs. P. has always been an over-anxious woman, a perfectionist who sets very high standards for herself and is always inclined to ruminate about what she sees as her failings.

She became depressed shortly after the birth of her second child, ten months before being seen. She began to worry excessively and continuously over the idea that she was not clever enough for her husband, that she was not looking after her home properly, and that her bathroom was continually in need of cleaning. She spent most of the day thinking about these ideas and repetitively cleaning the bathroom. Treatment with imipramine by her general practitioner made her feel more depressed, since she felt that while taking this drug she could get through even less work than before. She was given isocarboxazid 10 mg and chlordiazepoxide 5 mg three times a day. Depression lifted and her fears and excessive worries ceased. But she remained an anxious personality always prone to worry excessively for little reason.

A MAO inhibitor may also be helpful in overcoming depressive symptoms, and particularly the apathy and lack of drive, which sometimes occur in schizophrenic patients whose psychotic symptoms are controlled by a phenothiazine derivative. There is a lift of mood and increased activity and drive and emotional contact when a MAO inhibitor is added to the phenothiazine. But caution needs to be exercised for MAO inhibitors may cause an exacerbation of schizophrenic symptoms.

TREATMENT WITH COMBINED ANTIDEPRESSANTS

Dextroamphetamine, combined with a MAO inhibitor, is sometimes effective in dealing with depressive anergia unresponsive to the MAO inhibitor alone. Although there have been reports of adverse reactions[181], such as a hypertensive crisis, following the use of this drug combination, in practice the risk is very small when the amphetamine compound is given by mouth. Sometimes tolerance to the amphetamine develops, and rather than increase the dose it is better to change to tranylcypromine, 10–20 mg a day.

Mrs. S., aged 44, complained of excessive tiredness, irritability, difficulty in concentrating on her work, loss of interest, difficulty in getting to sleep except with a hypnotic and then waking after about

4–5 hours, a tendency to worry excessively over relatively minor matters, and a continual sense of guilt over her husband's death. These symptoms were always worse in the latter part of the day. They had gradually developed after the death of her alcoholic husband two years before.

Drinamyl, up to four tablets a day, helped her at first but gradually ceased to be effective. Phenelzine 15 mg, three times a day improved concentration and lessened irritability and the sense of tension, but did not give her more energy. Two tablets a day of Drinamyl were added and brought about some improvement, but only when tranylcypromine, 10 mg once a day, was given with phenelzine 15 mg twice a day did she begin to feel like her former self. Tranylcypromine alone, depending on the dosage, proved to be either inadequate or over-stimulating, in spite of the addition of a tranquilliser.

The combination of a *MAO inhibitor with amitriptyline* is discussed on p. 52.

Treatment with MAO inhibitors

Dosage The effective dosage of each MAO inhibitor varies from patient to patient. It is important to find as quickly as possible the right dosage. Too small a dose will be ineffective, too large a one may cause more harm than good because of side effects. But sometimes it proves difficult to give an effective dosage of a MAO inhibitor because the patient is unable to tolerate the drug's side effects. Changing to another MAO inhibitor will sometimes solve this problem.

Average starting doses and dosage range for each MAO inhibitor are indicated in Table II.

TABLE II

Average starting doses and dosage range

MAOI	*Usual starting dose*	*Dosage Range*
Iproniazid (Marsilid)	50 mg tds	25–200 mg a day
Isocarboxazid (Marplan)	10 mg tds	20–40 mg a day
Mebanazine (Actomol)	5 mg tds	10–30 mg a day
Nialamide (Niamid)	50 mg tds	75–300 mg a day
Phenelzine (Nardil)	15 mg tds	15–60 mg a day
Phenoxypropazine (Drazine)	5 mg tds	5–20 mg a day
Tranylcypromine (Parnate)	20 mg on waking 10 mg at noon	10–60 mg a day

Relapse after an initially good response may occur for a number of reasons:

(*a*) Improvement is largely due to a "placebo response", which usually declines after two or three weeks.
(*b*) The initial response is related to the initial sedating effect of the MAO inhibitor and tension symptoms return as this wears off. If this is the case the patient may respond better to one of the other group of antidepressant drugs.
(*c*) Increased anxiety and depression may occur when difficulties worsen or a change of doctor occurs. The drug should be continued and, if necessary, the dosage temporarily increased.
(*d*) The dosage of the MAO inhibitor has been reduced too much. When side effects are troublesome this may be unavoidable and it is then better to change to another MAO inhibitor.

Treatment with a MAO inhibitor needs to be continued until the depressive illness has fully resolved. There is no convincing evidence that treatment with the drug, although it may result in the total disappearance of symptoms, does more than suppress outward signs of the illness. It does not appear to shorten the duration of the depressive illness itself, although the drug will help to clear up secondary symptoms which may have arisen and are often so troublesome to shift.

A MAO inhibitor must therefore be continued until the expected spontaneous remission which characterises depressive illness occurs. If the drug is stopped too soon symptoms will begin to return. In practice the dosage of the drug is lowered and stopped over three weeks about every three months, the full dosage being immediately resumed if symptoms start to recur. A close watch on the patient over the next six months is important for it is during this time that a relapse is most likely.

With some patients the dosage of MAO inhibitor can be progressively reduced to 15 mg phenelzine, or its equivalent, a day, but any attempt to stop the drug altogether results in symptoms returning. These patients appear to need this small daily maintenance dose in order to function effectively. Some patients have now followed this treatment regime for over seven years. That it is not simply a placebo effect is shown by the way symptoms gradually return when the MAO inhibitor is substituted by an inert but identical looking tablet.

Where phobic symptoms have been present for a long time, perhaps many years, the combination of a MAO inhibitor and a tranquilliser will have to be continued for anything up to two years in order for undesirable habits to be broken and relearning to occur. Table III illustrates this point.

Treatment along these lines with a MAO inhibitor, as with

imipramine, has been criticised on the grounds that ECT would remove depression radically so far as the individual attack of depression is concerned. But it is particularly in these reactive depressions that ECT is least effective, and may even be harmful in the sense of producing memory upset or feelings of depersonalisation. Even when it is effective patients may subsequently relapse and need further treatment. However, there certainly are times when ECT should not be withheld.

TABLE III

Phobic Anxiety

Age and sex of patient	*Length of Phobia*	*Main Phobia*	*Length of drug treatment*
48 (M)	6 yrs	Thunder	18 months
39 (M)	5 ,,	Travel	9 ,,
42 (M)	5 ,,	Travel	8 ,,
34 (M)	6 ,,	Travel	18 ,,
49 (M)	10 ,,	Tremor	19 ,,
40 (M)	6 ,,	Travel	14 ,,
48 (M)	5 ,,	Telephone	5 ,,
38 (F)	4 ,,	Tremor	14 ,,
47 (F)	8 ,,	Travel	20 ,,
66 (F)	46 ,,	Travel	24 ,,

Criticism has also been made of antidepressant drug treatment on the grounds that the drugs interfere in some way with the natural tendency of depression to recover. Exactly the same criticism was made in the past of ECT, and in both instances it seems to be based more on prejudice than on convincing clinical evidence. Equally, the idea that treatment with these drugs or ECT is more likely to lead to relapse in the future is totally lacking in factual support.

COMBINED TREATMENT WITH ECT AND A MAO INHIBITOR

If depression is deep and there is a risk of suicide ECT should never be withheld. It may also be required if depressive symptoms have not responded to drug therapy after a reasonable trial. There is no increased risk from giving ECT to a patient already taking a MAO inhibitor despite earlier warnings, although the anaesthetist obviously needs to know this fact in case a rare cardiovascular collapse should occur and the need to give a pressor amine arises.

There is inconclusive evidence that combining ECT with antidepressant drugs may reduce the number of ECT needed, provided of course that the drug has been given for at least ten days continuously before starting ECT. For example, comparison of the number of ECT given to patients during recurring attacks of depression

shows that slightly fewer ECT are required to terminate an attack when the patient is also receiving a MAO inhibitor compared to when he receives ECT alone.

TABLE IV

Number of ECT needed, with and without antidepressant drugs

Patient	*No. of treated attacks*	*Av. no. of ECT per attack without antidepressant*	*Antidepressant*	*Av. no. of ECT per attack with antidepressant*	*No. of treated attacks*
Female	2	5	Imipramine	3	2
Female	1	10	Imipramine	5	1
Female	1	6	Imipramine	2	1
Male	6	6·5	Iproniazid	3	2
Female	2	4	Phenelzine	3	1
Female	2	5	Imipramine	3	2
Female	3	7	Tranylcypromine	4	1

It is well recognised that manic depressive patients respond poorly to ECT given in the early stages of a depressive attack, although symptoms will lift fully if ECT is given towards the end of the attack. Again the evidence is inconclusive, but it seems that in some instances, if an antidepressant drug is given for at least a fortnight before treatment, a patient in the early stages of a manic depressive attack will now respond to ECT. The antidepressant drug must be continued throughout the anticipated period of the attack, however, or relapse is likely to occur.

Do the drugs merely lift the level of depression, so that ECT now becomes effective? Or do they act by maintaining improvement following ECT? Is there any link up here with what sometimes occurs after a manic depressive patient has been treated by modified leucotomy? After leucotomy the patient may still experience attacks of depression, but these are now usually less severe[17] and respond more readily and fully to antidepressant drugs alone, or to ECT.

Mrs. H. had a history of manic depression, starting at the age of 24. Attacks of depression developed every autumn and lasted six months, to be followed by a period of mild hypomania. After the age of 40, depression extended and eventually became continuous and unresponsive to ECT or antidepressant drugs, alone or in combination. Depression

lifted after a modified leucotomy, but tended to recur in a mild form each autumn. These bouts of depression now responded fully to antidepressant drugs.

SIDE EFFECTS OF MAO INHIBITOR

Many side effects occur and are directly related to the dosage and to the therapeutic efficacy of the compound. Thus, of the hydrazine MAO inhibitors, iproniazid has the highest frequency of side effects, nialamide the lowest. Side effects include the following:

Postural and orthostatic hypotension, causing dizziness, unsteadiness and falls, particularly in elderly patients. Hypotension may occur suddenly and lead to orthostatic collapse. Dextroamphetamine 5–10 mg a day occasionally seems to help some patients. Simpson[179] suggests using ephedrine $\frac{1}{4}$ gr (16 mg) twice a day. When symptoms are severe the dose of the MAO inhibitor must be reduced or the drug stopped altogether.

Dry mouth, an unpleasant musty taste in the mouth, nausea, indigestion and constipation. Constipation will usually respond to mild laxatives.

Oedema of the ankles, and periorbital oedema, most obvious after sleep, is sometimes troublesome but will usually respond to diuretics. But the use of a diuretic may increase hypotensive side effects. *Flushing* of the face occurs, particularly with iproniazid. *Maculopapular rashes*, pustules and dermatitis occasionally occur, but do not usually require the drug to be stopped. Dryness of the skin is most common with tranylcypromine.

Micturition is sometimes affected. There is difficulty in starting or even retention, requiring catheterisation and stopping the drug. Atonic bladder musculature will produce dribbling at the end of micturition. Nocturia is sometimes troublesome and interferes with sleep.

Sexual disturbances usually take the form of impotence. In men erection occurs less often and there is delay or difficulty in ejaculation. This side effect is sometimes utilised in the treatment of premature ejaculation. Inability to achieve orgasm may also occur in women. These difficulties disappear when the drug is reduced in dosage or stopped. Occasionally increased libido occurs in both sexes.

Breathlessness, especially in older patients.

Sweating is most common with tranylcypromine.

Blurred vision, due to difficulty in accommodation. Red-green colour blindness occurred with pheniprazine (Cavodil), now withdrawn from use.

Neurological side effects include hyperreflexia, often manifesting only at night in the form of twitchings and jerks, tremor, peripheral neuritis and cramps. The presence of *peripheral neuritis* requires the drug to be stopped. Some of these symptoms may be due to a

deficiency of pyridoxine (vitamin B.6). 40–80 mg a day of pyridoxine may lessen or stop them. Epileptic fits can occur in predisposed patients[150].

Headache is most often described as a muzzy sensation or sense of tightness at the back of the head and neck. Severe headache occurs during a "hypertensive crisis".

Of the psychiatric complications, hypomania is probably the most common, occasionally developing into full mania. Patients become overtalkative, irritable and intolerant, tend to overspend and behave in a tactless or indiscreet manner unlike their usual selves. The MAO inhibitor generally needs to be stopped or the dosage reduced. However if overactivity is not too great the MAO inhibitor can be continued unchanged and combined with a drug such as haloperidol, chlorpromazine or lithium carbonate.

A woman of 32 developed depressive symptoms, brought on by marital stresses. Her mother suffered from manic depression, but the patient herself had shown no cyclothymic traits in the past. She responded rapidly to a combination of phenelzine and chlordiazepoxide. After a month she reported that she "felt better than she had done for years". However her husband reported that she was "quite impossible", that she was garrulous and constantly talking, and was aggressive in manner and overactive in a nonconstructive way. She was spending excessive amounts on clothes for which she had little need, and her whole manner and way of life had changed for the worse. She was going to bed late and waking early. If it continued, her husband said, he was going to leave home.

Phenelzine was reduced to 30 mg a day and chlordiazepoxide was changed to haloperidol 3 mg a day, with chlorpromazine 100 mg at night. Within a week the hypomanic state had subsided and she was eventually stabilised on a combination of phenelzine 15 mg and haloperidol 1·5 mg twice a day.

Psychopathic behaviour may be increased if a MAO inhibitor is given to a "psychopathic personality"[152]. Anti-social acts increase and aggressive behaviour may lead the patient into trouble.

A man of 26 who had drifted from job to job, never able to stick at any one of them for more than a few months, was seen complaining of depression and tiredness. He was prescribed tranylcypromine 30 mg a day. He became truculent and aggressive towards his parents with whom he lived, kept getting into fights at dance halls and amusement arcades, and was eventually arrested after smashing the front window of a cafe because the owner would not give him a cup of coffee for nothing.

A medical student was referred by his tutor because of increasing depression and anxiety concerning his forthcoming exams. He was given phenelzine and chlordiazepoxide. A month later he said that he

had "never felt better" and now saw no point in passing the final exams since he could have a much more enjoyable life as a student, and the authorities were certain to renew his grant for at least another year.

Schizophrenic symptoms may be exacerbated by MAO inhibitors. An undiagnosed schizophrenic may suddenly start to show florid psychotic symptoms. But although the presence of schizophrenia should lead to caution, the antidepressant drugs can be very useful in treating the recurring bouts of depression to which some schizophrenics on a maintenance dose of a phenothiazine drug are prone. This is particularly so in schizophrenics with well preserved personalities. Where there is flattening of affect and other signs of schizophrenic deterioration the antidepressant drugs have little to offer. Provided the patient is having an adequate dosage of a phenothiazine and is closely supervised, the risk of giving a MAO inhibitor is not great.

A toxic confusional psychosis may occasionally be precipitated, especially in older age groups. This usually requires the MAO inhibitor to be stopped temporarily, and chlorpromazine substituted, 50–100 mg three times a day. Loss of memory is complained of by some patients, particularly over recalling names and recent events.

Sleep may be reduced, particularly with tranylcypromine or if the last dose of the MAO inhibitor is given late at night. Vivid disturbing dreams sometimes occur.

TOXIC EFFECTS OF MAO INHIBITOR

Jaundice is the most serious complication. With iproniazid[148] the risk of jaundice has been estimated at about one in every 4–5000 patients treated, the mortality rate of affected patients being about 25 per cent[74,154]. The incidence of jaundice from the use of the other hydrazine MAO inhibitors is lower, although none is free of risk. Although there have been reports of jaundice following treatment with tranylcypromine[27] the risk of liver damage from this drug is probably very small.

In terms of pathology, MAO inhibitor induced jaundice is the result of hepatocellular damage and is virtually indistinguishable from the clinical and pathological picture that occurs in severe virus hepatitis. Floody[64] has suggested that the incidence of iproniazid induced hepatitis and viral hepatitis in the general population is of a similar order, although the damage caused by iproniazid is greater. Apart from a direct toxic effect on the liver, the MAO inhibitors may activate viral hepatitis, aggravate an already existing liver trouble or amplify the toxic action of other drugs. There is also the possibility that treatment with a MAO inhibitor may coincide with the development of infective hepatitis.

The occurrence of jaundice is unrelated to dosage or to the total amount of drug administered. Jaundice may occur at any time during treatment with a MAO inhibitor but is most likely to develop within the first six weeks.

Weekly serum glutamic oxaloacetic transaminase estimations were recommended at one time to detect early hepatic cellular damage. But by the time a significant rise is detected it is probably too late to prevent jaundice developing, particularly since the effects of the drug persist for up to two weeks after stopping it.

It is common sense, when jaundice has resulted from the use of a MAO inhibitor, to avoid giving these drugs again unless strong reasons exist for so doing. Holdsworth[89], after a study of MAO inhibitor induced jaundice occurring more than once in a number of patients, concluded that no MAO inhibitor should be given again after jaundice. But there are always exceptions to such a rule, as in the following example:

> The patient was a woman of 46, a top executive in an expanding fashion business. Since 1949 she had suffered from recurrent attacks of depression which have become increasingly severe and frequent. Until 1958, apart from a two year spell of psychoanalysis at the beginning, she was treated with ECT and just about managed to hold down her job. She was then given iproniazid and made a full and rapid recovery from all her depressive symptoms. She continued to take iproniazid regularly for eighteen months until she developed jaundice. All drugs were then stopped and she recovered within a month. Depression returned and she was given all the antidepressant drugs except iproniazid in turn without effect. ECT was given again but it was obvious that she was far from well. Eventually her directors told her that if the quality of her work continued to deteriorate she would have to retire. She thereupon asked to be given iproniazid again, although she was fully aware of the risk involved. Within a fortnight of resuming treatment with iproniazid her symptoms were gone and she was back to her former self. She has remained on iproniazid, with no sign of jaundice, for the past four years.

> A similar sequence of events occurred with a middle-aged woman who had been disabled by phobic anxiety until treated with isocarboxazid 10 mg three times a day and chlordiazepoxide. She developed jaundice after taking the drug regularly for one year. After recovering from jaundice phobic symptoms returned. Not until she was put on to a MAO inhibitor again, at her own request, and after full discussion of the risks, did these start to improve.

Blood changes are rare. Haemolysis has been reported to occur. A microcytic or normocytic anaemia sometimes develops; the aetiology is not clear but may be related to vitamin B.6 (pyridoxine) deficiency.

Interactions between MAO inhibitors and other drugs

The side and toxic effects of MAO inhibitors were quickly recognised. It is only comparatively recently, however, that the dangers of combining certain drugs and substances with the MAO inhibitors have become known and publicised.

Dangerous reactions occur if high concentrations of body amines, which are normally stored in a bound and inactive form (see p. 143), remain in a free and active form. This may either result from (*a*) excessive inhibition of MAO, which is particularly liable to occur during treatment with tranylcypromine, and to a lesser extent with other MAO inhibitors; (*b*) a flood of free catecholamines being released from their binding sites by substances such as amphetamine or tyramine, in conjunction with inhibition of MAO; or (*c*) prevention by a drug such as imipramine of the re-absorption of noradrenaline liberated at nerve endings. Normally 95 per cent of this liberated noradrenaline is inactivated by re-absorption into its storage sites. If a MAO inhibitor is also present a dangerous state may develop.

Dangerous reactions may also occur due to the fact that MAO inhibitors may affect other enzyme systems. For instance the effects of drugs such as pethidine and pentobarbital which are metabolised by liver microsomal enzymes, may be markedly potentiated during treatment with a MAO inhibitor due to these enzymes being inhibited by the latter.

The effect of high concentrations of free and active catecholamines is to cause a "hypertensive crisis", clinically resembling a phaeochromocytoma, or subarachnoid haemorrhage. Palpitations and a forceful increase in heart rate are usually the first sign, followed within a minute or less by a throbbing sensation in the neck, profuse sweating and a feeling of choking or suffocation. There may also be neck stiffness, photophobia and pains in the chest. Sometimes, if the patient immediately lies down and remains motionless for half an hour or so, these symptoms will gradually pass off. But in the majority of instances an intense thumping headache develops suddenly over the occipital and temporal regions which later becomes generalised. The patient may vomit, scream or writhe in pain, and is frequently terrified and convinced that he is going to die. The intense headache usually subsides after about half an hour, but an unpleasant dull ache may persist for some hours or even days and weeks afterwards. Occasionally further hypertensive bouts occur over the next few days; in one patient this was brought on by the exertion of running to catch a bus.

During such an attack the pulse rate usually slows but occasionally increases, and there is a marked rise of systolic blood pressure and a lesser rise of diastolic pressure.

Recovery is usually complete but intracranial bleeding may occur, sometimes with fatal results[60,124,190]. Death has also been reported due possibly to cardiac arrhythmia[198].

FACTORS BRINGING ABOUT A HYPERTENSIVE CRISIS

(1) *A hypertensive crisis may occur from the use of MAO inhibitors alone, particularly tranylcypromine.* It has been estimated that a hypertensive crisis occurs in about 1 in every 200 patients treated with tranylcypromine, and death in about 1 in 100,000 cases. On the other hand, about 2 per cent of patients taking tranylcypromine complain of some degree of headache at some time during this treatment.

It is impossible to predict a hypertensive crisis, and there is no age or sex discrimination. It is patients who react readily to the side effects of drugs, who have a reactive rather than an endogenous type of depression, who are most liable to develop this complication. Schizophrenic patients seem to be "protected" from this reaction.

(2) *Amphetamines* release active noradrenaline from its binding sites. Hypertensive crises have occurred when amphetamines and other stimulants such as methylphenidate and ephedrine have been given in combination with a MAO inhibitor. Except when they are combined with tranylcypromine, amphetamine and the other stimulant drugs do not constitute a serious risk when given orally. It is when the intravenous route is used that the chances of precipitating a hypertensive crisis are so great. *Methylamphetamine should never be given intravenously to any patient taking or who has taken a MAO inhibitor within the previous fortnight*[47].

A man of 38, who had been taking phenelzine until eight days before, was given intravenous methylamphetamine. Within seconds of the injection he developed headache in the occipital region so severe that he cried out. He also complained of palpitations and a terrifying sense of constriction in the chest. His breathing was rapid and shallow, and he became pale, cold and sweaty.

His blood pressure rose immediately from 120/80 to 280/150 and remained at this level for an hour. Two hours later it was 210/110, and after four hours had fallen to 180/90. His headache was then still severe but was now bearable. Twenty-four hours later the pressure was 150/80 and had returned to its normal level by the next day.

(3) *Foodstuffs may interact with MAO inhibitors*

(*a*) *Foods containing tyramine*[8,20,21,93,181]

Tyramine exerts its pressor activity mainly by releasing adrenaline and noradrenaline from their storage sites. All types of *cheese* except cream and cottage cheese contain large amounts of tyramine. Beer and wines contain only small amounts with the exception of *chianti.* Yeast extracts such as Marmite contain significant quantities of

tyramine (and also histamine), as does game which has hung for some time, and pickled herrings[135]. Reactions have also occurred after eating tinned tunny fish, brisling, salmon, herrings in oil and reindeer.

(*b*) *Foods containing dihydroxyphenylalanine (DOPA)*[19,126]

DOPA exerts considerable pressor activity in patients given MAO inhibitors.

Although broad bean seeds do not contain much DOPA, this aminoacid is present in high concentration in the pods. Sliced broad beans have been reported to cause a hypertensive crisis.

(*c*) *Coffee and bananas* have also been incriminated, but the evidence for this is unconvincing.

(4) Hypotensive drugs such as *guanethidine* and *alpha-methyldopa* (Aldomet) may react dangerously with MAO inhibitors, since both these compounds release catechloamine from binding sites [188].

(5) Theoretically *reserpine* and other rauwolfia preparations could cause a hypertensive crisis when combined with MAO inhibitors. However, reports of the interaction of reserpine and a MAO inhibitor describe states of mania and excited confusional states rather than hypertension[71,191].

TREATMENT OF A HYPERTENSIVE CRISIS

There is a striking similarity between these symptoms and those which occur in phaeochromocytoma. It is reasonable to assume that the crisis is the result of noradrenaline being released from adrenergic nerve endings and to treat it, if possible, by an adrenergic blocking agent such as phentolamine 5 mg intravenously, and chlorpromazine 50 mg intramuscularly.

If the hypertensive crisis follows the ingestion of a yeast extract, the patient should also be given an antihistamine drug intravenously.

Sedatives may also be needed.

Other dangerous reactions

Imipramine inhibits the re-absorption of noradrenaline released at nerve endings onto binding sites. If MAO should be inhibited, free and active amines therefore steadily build up in the brain. This situation occurs when imipramine is given to a patient who is taking, or has taken within the past fortnight, a MAO inhibitor. An alarming reaction sometimes results, and this is most likely when the MAO inhibitor is tranylcypromine. The reaction ranges from nausea, dizziness and sweating to tremor, hyperpyrexia, delirium, excitation, rigidity, convulsions, coma and occasionally death[25,140,180]. It is because of the possibility of such a reaction that a drug-free interval

of one to two weeks is recommended when changing from a MAO inhibitor to imipramine.

A girl of 24 with agitation and depression was given imipramine 50 mg twice a day and phenelzine 15 mg three times a day. After four days she complained of headache, dizziness and sweating and some hours later had a series of convulsions. She was unconscious for two hours, but eventually made a full recovery.

A woman of 74, dying of carcinoma of the bladder, was given tranylcypromine for a week. Her depressed mood failed to improve and tranylcypromine was therefore stopped and immediately replaced by imipramine. After the third dose of 25 mg she started to sweat, developed generalised rigidity and neck stiffness and gradually became comatose and died after about twelve hours. At post mortem no cause of death or of these neurological signs was found.

There is no specific treatment. Antidepressant drugs should be stopped, hyperpyrexia and convulsions controlled, and respiration maintained. Intravenous chlorpromazine may be helpful during the restless stage, and prednisolone if the patient becomes unconscious.

Amitriptyline and nortriptyline are reported to cause similar reactions in combination with MAO inhibitors. But in clinical practice the risk seems very small when these drugs are combined with a hydrazine MAO inhibitor and given by mouth, while the advantages may be great[143] (see p. 52). It is probably best to avoid combining tricyclic antidepressants with tranylcypromine, except in therapeutically resistant cases.

Analgesics—pethidine and morphine[147,177,183,186]

When pethidine is given to a patient receiving a MAO inhibitor, particularly those which also inhibit non-specific oxidase such as iproniazid, phenelzine and tranylcypromine, a dangerous reaction may rapidly ensue. The danger is all the greater if pethidine is given parenterally. Within minutes of an injection the patient will start to sweat and show signs of cerebral excitement, shiver, eventually collapse, become unconscious and die.

Many reports of such severe reactions have been published. The usual story is that the patient has been treated for depression with a MAO inhibitor for a long period by a psychiatrist and is given pethidine during an acute emergency by a surgeon, obstetrician or anaesthetist.

The effects of pethidine are potentiated by MAO inhibitors, which inhibit microsomal enzyme systems within liver cells and thus reduce the rate of metabolic inactivation of pethidine[181].

Treatment of the condition calls for prompt acidification of the

urine, since the excretion of pethidine is increased in highly acid urine. Prednisone should also be given, in addition to other standard methods of resuscitation[120].

It has been suggested that if pethidine is likely to be needed by a patient taking MAO inhibitors, his sensitivity to the drug should be tested[40]. The method is to give 5 mg of pethidine intramuscularly and record blood pressure, pulse, respiration and level of consciousness every 5–10 minutes for an hour. At the end of this period, if there has been no obvious reaction, 10 mg of pethidine is given and the whole procedure repeated. At the end of the second hour 20 mg is given, then 40 mg and so on. In cases of emergency the procedure can obviously be speeded up.

The actions of morphine, morphine-like analgesics, and amidone may be similarly potentiated by MAO inhibitors and small doses only should be given initially in an emergency.

Cocaine and procaine

There is some evidence, both from animal experiments and clinical reports, that these drugs may also be potentiated by MAO inhibitors[41].

Phenothiazines

The action of phenothiazine derivatives may be prolonged and enhanced[52]. One result of this may be increased extrapyramidal reactions.

> A woman of 58 with paranoid and depressive symptoms was given tranylcypromine 30 mg, trifluoperazine 10 mg and orphenadrine 100 mg a day. Her symptoms improved but she became restless, developed a Parkinsonian-type rigidity, and eventually began suddenly and momentarily to lose consciousness and to fall. Reducing the trifluoperazine lessened these effects but led to the partial return of her original symptoms. Only when tranylcypromine was reduced to 10 mg a day, and the trifluoperazine continued at 10 mg a day, was she totally free of symptoms and side effects.

Barbiturates[115] are potentiated by MAO inhibitors, although in practice this effect is not marked.

The effects of alcohol[173] are potentiated by MAO inhibitors. It is particularly important to warn car drivers of this.

Insulin

MAO inhibitors, particularly mebanazine, appear to possess a hypoglycaemic action, and to potentiate the hypoglycaemic activity of insulin. It has been suggested that this action occurs as a result of the MAO inhibitor interfering with the compensating hypoglycaemic adrenergic response to a fall in blood sugar [187,195].

Special psychiatric syndromes helped by MAO inhibitors

MANIC DEPRESSION

Generally manic depressive states do better with imipramine or amitriptyline than with one of the MAO inhibitors and these drugs should be the first choice of treatment. But there is a type of patient with manic depressive illness who does better with a MAO inhibitor, in particular iproniazid, combined with lithium carbonate or haloperidol. Such a patient has usually shown immature reactions and marked hysterical traits since adolescence, and swings of mood have been superimposed on this immature personality.

Mrs. T. had first become depressed twenty-two years earlier, immediately after the birth of her first child. After four months, depression had been followed by hypomania. Since then she had exhibited mixed fluctuating depressive and hypomanic symptoms. She was irritable, querulous, constantly and loudly complaining of her husband's impotence and of her own numerous physical symptoms, went to bed before 9 p.m. and got up around 4 a.m. worked at fever pitch for up to twelve hours continuously and then retired to bed for several days, and was constantly taking up and discarding new hobbies and interests. During exacerbations of depression she had been given ECT without much effect other than upon her memory.

She was given iproniazid, 50 mg three times a day, and haloperidol, 1·5 mg twice a day. After a fortnight she was calmer and more stable in mood, but because of hypotensive side effects iproniazid was reduced to 25 mg three times a day. She has remained on this combination for the past four years, the dose of iproniazid varying between 50 and 100 mg a day depending upon her mood. Both Mrs. T. and her husband report that she has been considerably improved by this therapy.

In addition to frank manic depressive illness iproniazid is also valuable in treating some of the difficult cases of anorexia nervosa-like conditions which occur in middle-aged women associated with depression.

Mrs. W., aged 43, lost her appetite three years before treatment, after learning that her husband had had a short-lived affair with another woman. Her weight fell from 9 st. 10 lb. to 6 st. 1 lb., and her periods became scanty and irregular. Treatment by her general practitioner with a variety of drugs, including amitriptyline and phenelzine and numerous tranquillisers, failed to improve her condition. When seen she looked and felt miserable and said that she had no appetite for food and was unable to make herself eat.

She was put on to iproniazid, 50 mg and chlordiazepoxide, 5 mg both three times a day. Although the dosage of iproniazid had to be halved after a fortnight, due to postural hypotension, her appetite began to improve and her weight rose steadily by about 2 lb a week to 9 st. Depressive symptoms also lifted. Iproniazid had to be continued for almost a year.

PARANOID STATES

Paranoid symptoms may occur in a variety of mental disorders. A common paranoid condition is what has been called the morbid jealousy or erotic jealousy syndrome[132,178]. Patients develop a pathological and usually unjustified jealousy towards their spouse, often in a setting of depression. The delusion is usually monosymptomatic and without evidence of schizophrenia. Depressive symptoms when present are usually of the reactive type, difficulty in getting to sleep, depression worse in the evenings and so on. Treatment with chlorpromazine often upsets these patients, and a piperazine phenothiazine is better in relieving their tension. But depression usually remains and with it the delusional jealousy. Adding a MAO inhibitor to the tranquilliser causes both depression and delusion to disappear. The combination appears to be what is so effective. Giving the MAO inhibitor alone may lift depression but at the same time increase tension, with the result that the patient may act out his delusional fears. Once symptoms are controlled the dosage can slowly be reduced, but a maintenance dose is usually required for a year or more.

J. was aged 31 when first seen. For a year he had had vague but increasingly strong suspicions that his wife was unfaithful to him. He admitted that these suspicions were totally unfounded and that his wife was a devoted wife and mother to him and their two children. None the less his suspicions continued and began to affect his mood and his relationship with his wife. He felt compelled to ask his wife where she had been, to whom she had spoken, to search her handbag, her private drawers and even her clothing for signs of infidelity. She reacted by becoming angry and eventually threatened to leave him unless he sought medical advice.

When first seen he was clearly depressed and was preoccupied with thoughts of his wife's behaviour. His work had suffered, he always felt tired and he was experiencing bouts of severe anxiety. He give a history of having been discharged from the Army at the age of 20 because of psychoneurosis.

Symptoms responded rapidly to a combination of phenelzine 15 mg three times a day and trifluoperazine 5 mg twice a day. On trifluoperazine alone he had no suspicions about his wife but felt tired and lacked interest and energy. On phenelzine alone he was tense and irritable. He has needed to continue these drugs over the past four years, for symptoms quickly return when they are stopped.

HYPOCHONDRIASIS

Recent studies of hypochondriasis have emphasised how often depression or anxiety states underlie hypochondriasis. An antidepressant drug combined with a tranquillising drug may sometimes effect considerable improvement. Facial pain in particular will often respond dramatically to a combination of a MAO inhibitor

and a tranquilliser[113,193]. A small dose of a piperazine phenothiazine, say perphenazine 2 mg three times a day, is usually better than a minor tranquilliser like chlordiazepoxide, unless phobic anxiety is prominent.

A woman of 36 was investigated by several hospital departments before being referred for a psychiatric opinion. She complained of pain over her nose and left side of her face, which had developed eighteen months before, after being struck in the face by a ball. She wept profusely while describing her symptoms, which were those of reactive depression. Treatment with phenelzine 15 mg three times a day and perphenazine 2 mg three times a day led to a marked improvement in all her symptoms within a month. Subsequently she was encouraged to deal with her marital difficulties, which up to then she had felt to be insuperable. Phenelzine and perphenazine needed to be continued for six months.

In general, tranylcypromine seems to be more effective than the other MAO inhibitors when hypochondriacal symptoms are prominent and unshakeable.

A journalist of 37 was seen complaining of soreness of the throat, "swelling" of the neck, catarrh and an unpleasant taste, tightness of the chest, indigestion, constipation and abdominal discomfort, and various skeletal symptoms. These symptoms had first begun about ten years before, shortly after his mother's death, and had increased steadily since the birth of his only child four years ago. He was an obsessional, depressive personality unable to externalise considerable suppressed resentments.

His symptoms virtually disappeared after several weeks' treatment with tranylcypromine 20 mg in the morning, 10 mg at noon and perphenazine 2 mg three times a day.

When pain and hypochondriacal symptoms have persisted for years, the antidepressant drug often needs to be combined with ECT. ECT alone may relieve symptoms but all too often relapse soon occurs. The presence of hypochondriasis has long been associated with a bad prognosis from the point of view of ECT[86]; but when ECT is given in combination with the appropriate antidepressant and tranquillising drugs a proportion of these patients remain symptom free or greatly improved. It is usually necessary to continue the drugs in full dosage for at least a year or more in order to avoid relapse.

DEPRESSION SECONDARY TO ORGANIC DISEASE

Depression when secondary to organic diseases, such as disseminated sclerosis, arteriosclerotic dementia, osteoarthritis and so on, will frequently respond well to antidepressant drug therapy. In these conditions, the antidepressant drug will usually need to be continued indefinitely.

Comparison of MAO inhibitors

In the treatment of reactive forms of depression characterised by extreme tension, iproniazid is still the most effective MAO inhibitor. But in the majority of patients the later MAO inhibitors provide a satisfactory and generally safe form of therapy. In a comparative trial of MAO inhibitors[48], on a group of out-patients with predominantly reactive types of depression, 80 per cent of patients who responded to iproniazid also improved in some degree with isocarboxazid or phenelzine, and about 50 per cent with nialamide. However, taking patients who responded *fully* to iproniazid, only 40 per cent did equally well with isocarboxazid or phenelzine, and considerably less with nialamide.

Isocarboxazid and phenelzine are comparable in their effects. In general, as a working rule, it is fair to assume that if a patient fails to respond *at all* to proper treatment with a hydrazine MAO inhibitor such as phenelzine or isocarboxazid within a fortnight he is unlikely to do so with another MAO inhibitor. It is often better to change without delay to imipramine or one of its analogues, or to give ECT.

Tranylcypromine, in addition to being a MAO inhibitor, also shows amphetamine-like effects which complicate its action.

General contra-indications for MAO inhibitors

General contra-indications for MAO inhibitors are:

(1) Marked endogenous depression features such as retardation, early morning waking associated with agitation and sweating, severe weight loss, suicidal impulses, and continuous self blame.
(2) Psychopathic personality.
(3) Schizophrenia (except under close supervision and given with large doses of phenothiazines).
(4) Receiving treatment with alpha-methyldopa (Aldomet), guanethidine, or a reserpine-like compound.

Individual MAO inhibitors

(*a*) IPRONIAZID (MARSILID)

This drug was the first MAO inhibitor to be used as an antidepressant. It is particularly useful in the treatment of reactive types of depression accompanied by long-standing and often severe tension.

Mrs. P. had been disabled by severe anxiety and bouts of depression for almost twenty years. During exacerbations she trembled, sweated,

lost weight, developed numerous somatic-anxiety symptoms, and felt so miserable and hopeless that on three occasions she made suicidal attempts, the last one of which almost succeeded. ECT and numerous combinations of drugs had failed to help, and modified leucotomy was being considered when she was prescribed iproniazid 50 mg and amylobarbitone sodium 60 mg, three times a day. After a fortnight symptoms were less and she felt more confident and able to do more than she had for years. Six years later she still requires to take iproniazid, but is now leading a normal active life.

Iproniazid is also useful in the treatment of manic depressive illness occurring in patients whose basic personality is immature and coloured by hysterical traits, not only in resolving symptoms, but in helping to stop recurrences by means of a small maintenance dose.

Reports that iproniazid caused severe and sometimes fatal liver damage aroused alarm and led to the drug being withdrawn in the U.S.A. In the U.K. the drug is still widely used, for there are severely disabled patients, like the woman above, who respond only to iproniazid and who relapse when the drug is stopped or substituted by another MAO inhibitor.

(*b*) PHENELZINE (NARDIL), ISOCARBOXAZID (MARPLAN), NIALAMIDE (NIAMID), MEBANAZINE (ACTOMOL), PHENOXYPROPAZINE (DRAZINE)

All these MAO inhibitors are hydrazine derivatives. Phenelzine and isocarboxazid are, overall, probably the most effective of these drugs. Nialamide, which differs structurally from the other hydrazines in possessing a benzyl carboxamide group, is not so effective although, not unexpectedly, side effects from it are minimal[9].

All these drugs tend to influence other enzyme systems, in addition to MAO, but isocarboxazid seems to do so less than the others[143]. It may be for this reason that jaundice following the use of isocarboxazid appears to be rare.

Isocarboxazid is less liable to cause side effects than phenelzine and is, for this reason, a better drug to use in those patients who are liable to react excessively to the side effects of a drug.

(*c*) TRANYLCYPROMINE (PARNATE)

Tranylcypromine is not a hydrazine derivative and structurally it is similar to amphetamine. It influences a number of enzyme systems apart from MAO. Clinically it shows amphetamine-like effects in addition to the MAO inhibitors characteristics described above[151]. The amphetamine-like effects usually appear quickly, within 24–48 hours and, like amphetamine, seem to be of a general euphoriant and stimulant rather than a specific antidepressant nature. If given too late in the day the drug may cause insomnia but, unlike amphetamine, appetite is not suppressed and weight is more likely to be gained than lost.

Perhaps because of these mixed effects, tranylcypromine forms a clinical bridge between the hydrazine MAO inhibitors and imipramine. It is particularly effective in those common mild depressive states which frequently show a mixture of endogenous and reactive features and where tiredness and lack of energy are prominent.

Analysis of the symptoms of out-patients who have responded well to tranylcypromine (Table V) shows mild depression of mood and loss of interest, a sense of fatigue and tiredness, and numerous bodily aches and discomforts. Body build tends towards mesomorphy or endomorphy.

TABLE V

Symptom analysis of 50 patients responding fully to treatment with tranylcypromine, phenelzine or imipramine

	Tranylcypromine	*Phenelzine*	*Imipramine*
Sleep disturbance — Early	70%	72%	33%
Sleep disturbance — Late	7%	5%	66%
Depression worse in first half of day	7%	4%	58%
Weight loss more than 7 lb.	20%	15%	54%
Sweating on wakening	34%	10%	62%
Phobic symptoms	30%	45%	25%
Hypochondriasis	59%	18%	12%

Because of its stimulating nature, patients who are already tense may become agitated and upset by tranylcypromine. The addition of a tranquilliser will sometimes prevent this, and it is common practice to prescribe a mixture of trifluoperazine 1 mg with 10 mg of tranlycypromine.

Unlike amphetamine, tolerance does not develop. But habituation and occasionally true addiction occurs[116]. It is suggested that tranylcypromine can precipitate a porphyrinuric crisis[1a].

(*d*) EUTONYL (PARGYLINE)

Although a MAO inhibitor, this drug's antidepressant activity is weaker and less predictable than tranylcypromine. It is not used used clinically as an antidepressant but only as a hypotensive agent.

Side effects resemble those of other MAO inhibitors. Psychotic reactions[184] can develop in predisposed individuals treated with eutonyl. The drug should be stopped immediately and a phenothiazine such as chlorpromazine given.

(3) THE TRICYCLIC ANTIDEPRESSANT DRUGS

(*a*) *Imipramine and its analogues*

Imipramine is an iminodibenzyl derivative, analogous in chemical structure to phenothiazine, and in fact synthesised in the search for a successor to chlorpromazine. It was during a trial of the drug on a group of schizophrenics that Kuhn[109] recognised its antidepressant action, a finding which led to its introduction into clinical psychiatry in 1957. It is the prototype of the tricyclic compounds, so called because their molecule includes three cyclical groups.

MODE OF ACTION

Impramine does not act as an inhibitor of MAO, nor does it produce excitation in normal human subjects or in animals. For a long time its mode of action remained unknown, but it is now believed that imipramine acts by inhibiting the re-absorption on to binding sites of noradrenaline released at nerve endings in the central nervous system[143]. Normally over 95 per cent of this noradrenaline is inactivated by re-absorption back on to its storage sites (see p. 144). Imipramine therefore causes the concentration of active noradrenaline at receptor sites to increase.

Imipramine will, like MAO inhibitors, counteract or reverse the sedative effects of reserpine, without influencing the release of brain amines. It has been suggested that the active effects of imipramine come from one of its major metabolites, desipramine[33]. Clinical trials with this drug have been disappointing, however. Imipramine has anticholinergic effects which accounts for some of its common side effects.

CLINICAL EFFECTS

In the course of his investigation Kuhn treated over 500 patients with imipramine. He found that the best results occurred in patients with endogenous depression, 70–80 per cent of whom improved on imipramine. Equally favourable results were obtained by later investigators[15,104] and it is now generally agreed that it is patients with mild endogenous depressive illnesses who respond best to imipramine and its analogues.

An endogenous depressive illness is characterised by diurnal variation in mood, improvement occurring as the day wears on, by the patient waking in the early hours of the morning often sweating profusely and worrying about the future, feelings of self-blame and of guilt, loss of appetite sometimes leading to a marked drop in weight, loss of libido, and varying degrees and mixtures of retardation and agitation. Hypochondriacal and paranoid delusions may also occur.

When symptoms are severe, if there is marked agitation, loss of several stones in weight, or if delusions are prominent, drugs alone are unlikely to be effective and ECT should never be withheld. Imipramine is most likely to be beneficial in mild endogenous forms of depression, particularly when there is retardation *without sign of excessive agitation.*

The initial effect of imipramine is sometimes unpleasant and for the first three or four days the patient may feel even more miserable than before starting treatment. But after about a week on the drug, in a successful case, the patient begins to feel relief. Mood begins slowly to lift, interest and ability to concentrate return, appetite and disturbance of sleep improve, and he feels that he can again cope with meeting people and his responsibilities. These improvements are usually slow, often continuing for several weeks, and may be partial or complete.

Depressive symptoms, as with the MAO inhibitors, are suppressed, not cured, by imipramine. It is therefore essential to continue the drug as long as the underlying depressive illness continues. If the drug is stopped prematurely symptoms will return. Endogenous depression is an illness which tends to resolve itself spontaneously, commonly between six months and two years. If a patient has had past depressive episodes these will often give an idea of the time the depression can be expected to last.

To avoid relapse, it is best to continue imipramine in a therapeutic dose for at least three months after symptoms have lifted. If there are still signs of underlying depression the drug must be continued until they disappear. In order to assess the situation the dosage of imipramine can be gradually reduced every three months. In some cases it will be found possible to stop the drug altogether, the depression having resolved. Other patients will still need to continue the drug, perhaps with a reduced dosage, to keep symptoms suppressed. Some patients need to continue on imipramine for up to two years or more, particularly those in the older age group, who have a marked tendency to relapse.

It is also advisable for patients with manic depressive or recurrent depressive attacks, when these occur frequently, to continue on a small maintenance dose of imipramine following recovery. This in itself may sometimes prevent an attack from manifesting itself. But if symptoms begin to recur the patient himself, without delay, can increase the dose of imipramine to the level at which symptoms are suppressed. Alternatively, those patients who are able accurately to anticipate a depressive attack may start taking imipramine about a month beforehand in order to abort it.

There is no contra-indication to giving imipramine with ECT. In fact, provided the drug has been taken for at least a fortnight before starting ECT, there is evidence that imipramine can reduce the

number of shocks needed. (See Table IV, p. 31.) There is also evidence for believing that when electro-convulsive treatment has been effective in lifting depression, giving imipramine subsequently will lessen or prevent the likelihood of relapse. Again it is probably prudent to give the drug for at least three months and then go through the procedure described above. Imipramine may also render a manic depressive patient, previously refractory to ECT given at the start of a depressive attack, responsive to ECT.

The recent Medical Research Council trial[129] showed that the action of imipramine is slower than that of ECT but that the two treatments are eventually comparable in their effects. Thus, twenty-five depressed patients treated with ECT were ready for discharge from hospital after five weeks, compared to only twelve imipramine treated patients. By the end of twelve weeks, however, thirty-four patients of each group had recovered sufficiently well to be discharged.

Therapeutically the drug seems to have similar antidepressive effects to ECT, but because of its slowness of action, particularly in severe depressive states, it has not replaced ECT. If depression is severe, or a patient's response to antidepressant drugs incomplete, ECT should never be withheld. It is not uncommon nowadays for ECT to be withheld for an unduly long time, or for an insufficient number of shocks to be given so that the patient is left in a state of semi-recovery, to relapse later or to await spontaneous recovery[100].

Some degree of anxiety is usually present in a depressive illness. When this marked it is best to combine a tranquilliser such as trifluoperazine 1 mg two or three times a day, or chlordiazepoxide 5–10 mg three times a day, with imipramine for the first month of treatment. Delay and Deniker[53] prefer levomepromazine for this purpose and claim that patients failing to respond to imipramine alone do so when the two drugs are taken together. If there is severe anxiety or agitation, amitriptyline, an analogue of imipramine with greater sedating properties, may be more effective than imipramine.

Imipramine may also be valuable in less typical forms of depression. Many mild depressive illnesses present as neurotic states: anxiety, hypochondriasis and physical symptoms, phobias and hysterical reactions. These are manifestations of mild depressive illness which are mainly seen by general practitioners and often misdiagnosed. Yet a careful history will reveal that the patient has lost his zest and sense of enjoyment, that everything, work and play, is now a joyless effort, and that he feels too tired to bother about anything any more. Treatment with an antidepressant drug such as imipramine will restore the patient's former sense of interest and enjoyment of life.

It is not uncommon for depression to accompany painful physical disease states, particularly when these are of a chronic nature; for

instance rheumatoid arthritis, osteoarthritis, psoriasis, ulcerative colitis, peptic ulcer. When the patient is depressed his physical symptoms seem to increase tenfold and he is no longer able to bear with them. Yet when the depressed mood is lifted by means of an antidepressant drug, he is able to tolerate his physical disabilities and accept them more readily.

Mrs. G., aged 65, was attending the department of physical medicine because of osteoarthritis of both hip joints. The pain from her hip joints had become so severe that she was no longer able to move about freely and virtually lived in a wheel chair. Her husband had been forced to retire from his work prematurely in order to look after his wife and the home. The question of surgery had been considered but was thought to be undesirable because of her mental state. It was at this point that she was referred for a psychiatric opinion.

She was depressed, hopeless about her future, waking early and ruminating about the possibility of suicide, and had lost all interest in her surroundings. Her husband described her as "a changed woman, only interested in talking about herself".

She was treated with a combination of imipramine 150 mg a day, trifluoperazine 3 mg a day, and amylobarbitone sodium 200 mg at night. After one month she was considerably more cheerful and outgoing, was doing much more in the house and no longer felt overwhelmed by pain.

Bradley[26] has demonstrated, in a study of thirty-five patients with pain, how pain either lessened as a symptom or disappeared altogether when depression was treated and lifted.

Depression may accompany or mask early dementia, particularly when this is due to arteriosclerotic changes in the brain. There is no means of reversing or stopping the process of dementia, but treatment of the accompanying depression may produce a significant improvement in the patient's performance. An antidepressant drug is obviously to be preferred to ECT, not only because of the need to avoid increasing memory difficulties but also because relapse into depression is likely after ECT alone.

A man of 68 began to grow forgetful. He was unable to recall the names of his friends with any certainty, and could no longer be relied upon to help his wife with the shopping. He read the newspaper but could not discuss current events intelligently as he had done in the past. He became irritable and dirty in his habits, and his wife found him increasingly difficult to manage in the house. He sat staring out of a window for much of the day, apparently noticing little.

Testing and investigation gave evidence of dementia, which was thought to be due to cerebral arteriosclerosis. On the supposition that he was also depressed he was given imipramine 150 mg a day. After ten days he was more active and cheerful, and had lost much of his apathy and irritability. The deficiency of memory remained but he now derived enjoyment from his activities and became a much pleasanter

companion to his wife. He remained on imipramine for a year until he died following a cerebral haemorrhage.

Imipramine (and amitriptyline) has a useful place in the treatment of nocturnal enuresis[149,155] in children and adults. 25–75 mg of imipramine given at night to a child of ten or more will sometimes result in complete cessation of bedwetting. Under ten years of age the dose of imipramine varies from 10 to 50 mg. With adults a single night-time dose may be insufficient and 25 mg imipramine twice a day may need to be given as well. It is important to give the drug long enough for the old habit to become firmly supplanted by the new pattern of behaviour, which usually takes between three and six months with children, and up to a year for adults.

Numerous studies, controlled and uncontrolled, have confirmed the effectiveness of imipramine in clearing up nocturnal enuresis.

DOSAGE:

The most usual therapeutic dose of imipramine is 150 mg a day in three divided doses. Excessive side effects may prevent the full dosage being given, and this is particularly likely in elderly patients.

The majority of patients who fail to respond to 150 mg imipramine a day will not improve if this dosage is doubled. However, there are a few patients whose symptoms will only respond completely to 225 mg or 300 mg imipramine a day. There is no advantage in going beyond this dose. Side effects are directly related to dosage.

Intramuscular imipramine is occasionally useful in patients who are severely retarded or stuporose, or are negativistic, although ECT is generally to be preferred. The dosage is 50 mg three times a day.

COMBINATIONS OF IMIPRAMINE AND OTHER DRUGS

(i) *Imipramine and ECT* (See p 48.)

(ii) *Imipramine and a tranquilliser.* This combination is advisable during the first month of treatment if anxiety or agitation are present. Imipramine alone may, paradoxically, increase these symptoms. When the patient is agitated,* chlorpromazine 25–50 mg three times a day, 100 mg at night, or chlordiazepoxide 10 mg three times a day are probably best. Trifluoperazine 1 mg three times a day is better when depression is accompanied by anxiety rather than agitation.

Imipramine may be helpful in dealing with the depression which sometimes occurs in phenothiazine treated schizophrenics. Caution should be exercised, for imipramine can exacerbate schizophrenic symptoms. But combined with an adequate dosage of derivative phenothiazine there is little risk of this occurring.

* *Anxiety* is a subjective feeling of fear. *Agitation* may include anxiety but is characterised by motor restlessness.

A combination of imipramine with haloperidol or lithium carbonate will sometimes control "mixed manic-depressive states" or "schizo-affective states", although in general amitriptyline is preferable to imipramine in such cases.

(iii) *Imipramine and Amphetamine.* Dextroamphetamine, 5–10 mg a day, may be useful during the first fortnight of treatment, not only to counteract side effects but also to potentiate the action of imipramine.

(iv) *Combined antidepressants* (See also p 62.)

Imipramine may be combined with one of its tricyclic analogues without risk. 50 mg or more of amitriptyline given with a hypnotic at bedtime, in addition to imipramine during the day, is useful in combating insomnia.

There are depressed patients whose symptoms do not respond to any one of the antidepressants or to ECT. On the assumption that two drugs are more powerful than one, the blunderbuss principle was applied to these drug-resistant patients and they were given combinations of imipramine or amitriptyline and a MAO inhibitor. It was quickly recognised that the side effects of each drug, particularly those due to hypotension, were potentiated by the other, and that caution was needed concerning dosage in individual cases.

After a time alarming reactions began to be reported. On these drug combinations some patients became restless, excitable, developed hyperpyrexia, convulsions, collapsed and occasionally died. As a result the Food and Drug Administration in the U.S.A., and the Witts Committee in the U.K., have issued warnings against using the two groups of drugs in combination.

Nevertheless, clinicians have continued to treat with combined antidepressants severely disabled patients who have failed to respond to any other treatment. They have found the combination to be effective in relieving certain symptoms when all else has failed. And provided precautions are taken and care exercised the risk of serious side effects occurring is small[49,66,169,170].

The type of patient who does particularly well with this combined antidepressant therapy tends to have symptoms of reactive depression, shows a good deal of anxiety, has lost a stone or more in weight, and frequently has somatic symptoms. He has often been ill for several years and yet has never given up struggling and forcing himself to carry on as well as possible.

Many of the reports of serious or fatal reactions have concerned suicidal attempts[96], when depressed patients have taken large amounts of both drugs. But it is also clear that imipramine[172], and probably to a much lesser extent, amitriptyline, may precipitate a serious or fatal reaction when combined with a MAO inhibitor. From the biochemical point of view such a reaction is only likely to

occur if the amine oxidase is completely inhibited and the catecholamine stores are full.

To minimise possible risks it is best to avoid using tranylcypromine in combination and to give a "pure" MAO inhibitor such as isocarboxazid. Both from animal experimental evidence and from clinical experience it appears that amitriptyline is safer than imipramine when used in combination with a MAO inhibitor, and is therefore to be preferred. Administration of either drug by parenteral injection should be avoided. Strict warnings to avoid alcohol, cheese and other tyramine containing foods should be given. Dosage of each drug should be carefully and individually adjusted to give the minimum side effects compatible with therapeutic effectiveness.

C.L., a man of 38, had suffered from depression, severe anxiety and phobic symptoms for nearly four years. He had forced himself to continue his work, but his marriage and private life had been seriously upset by his condition. MAO inhibitors, imipramine, amitriptyline, and numerous tranquillisers and sedatives had given him only temporary and partial relief. He had refused to have ECT. He was given amitriptyline 50 mg at night, and 25 mg twice during the day, together with isocarboxazid 10 mg and nealbarbitone 60 mg three times a day. After three weeks he was greatly improved, but because of postural hypotension amitriptyline was reduced by 25 mg. His symptoms continued to improve but it was not possible to reduce further the dose of either antidepressant drug without relapse occurring for the next five months. Over the course of the following two months first isocarboxazid, then amitriptyline, were reduced and stopped. He has remained well, only taking nealbarbitone when necessary.

Mrs. S. had complained of excessive tension and feelings of depression for several years. She was unable to get to sleep without a large dose of tuinal (400 mg), but in spite of this drug tended to waken after about four hours. She felt better on a combination of phenelzine 45 mg and chlordiazepoxide 30 mg a day, but symptoms did not fully lift until amitriptyline 50 mg was also given at night.

The increased risk of using tranylcypromine in combination with a tricyclic antidepressant is shown by the following example.

A man of 58 became depressed after retirement. He felt exhausted all day and slept heavily at night. Physically he was healthy. He was treated with MAO inhibitors, imipramine and amitriptyline in turn, with and without tranquillisers, but without much effect. ECT caused a temporary improvement only and upset his memory. He was given tranylcypromine, 30 mg initially, reduced to 20 mg after a fortnight, and amitriptyline 100 mg a day. A remarkable improvement occurred in his symptoms. A month later he became drowsy, began to sweat, and gradually became comatose. On admission to hospital his systolic pressure was 80mm. Full consciousness did not return for a week.

The value and the risks of combined antidepressant therapy must be carefully assessed and weighed in each patient. It is particularly useful for patients who are terrified of having ECT, or who react to ECT with anxiety and complaints of memory upset. Such patients in the past would only have tolerated ECT if given continuous narcosis at the same time. In many instances ECT can now be avoided, and better results achieved by giving amitriptyline 150 mg and isocarboxazid 30 mg a day, combined with heavy sedation for 10–14 days. (For this treatment the patient must be an in-patient.) Weight gain with combined antidepressant therapy is sometimes extreme.

Because the effects of MAO inhibitors persist for up to a fortnight after they have been discontinued, it is advisable, unless there are urgent reasons for not delaying treatment, to wait at least a week after stopping a MAO inhibitor, particularly if this is tranylcypromine, before changing to imipramine. The effects of imipramine do not persist so long, so that a MAO inhibitor may be safely given a few days after stopping imipramine.

(v) *Imipramine and barbiturates.* There is no contra-indication to combining a barbiturate with imipramine, although potentiation may occur. This is seldom extreme.

Depression is not uncommon in epileptic patients. Imipramine, or another antidepressant drug, can generally be given without needing to alter the dose of anti-epileptic drugs. But occasionally an antidepressant drug will increase convulsant tendencies and a temporary increase in dosage of anti-epileptic drugs will then be required.

(vi) *Imipramine and reserpine.* Imipramine and other tricyclic antidepressants inhibit, and even reverse, the sedating effects of reserpine in rats and mice.

There are theoretical grounds for believing that this combination may be effective in combating depression in man. Clinically, when reserpine is given to a depressed manic-depressive already treated for at least one week with imipramine, depression may lift suddenly within 4–5 days. The combination does not seem to be effective in other clinical forms of depression.*

O. had suffered from recurrent attacks of depression since the age of 19. For the past three years such attacks had occurred each spring and autumn, and lasted three months. In between attacks he was mildly hypomanic. Treatment with MAO inhibitors, tricyclic antidepressants and ECT had not helped to prevent or shorten the bouts of depression.

At the start of an attack he was given imipramine 150 mg a day. One week later reserpine 0·5 mg three times a day was added. Depression lifted suddenly after four days. The same treatment was repeated successfully in the following depression, six months later.

* Personal Research (Paper in preparation).

SIDE EFFECTS AND TOXIC EFFECTS

Common side effects. Many of the common side effects of imipramine and the tricyclic analogues are caused by their anticholinergic properties. It may be difficult, but important, to differentiate between drug effects and those due to the depressive illness.

A dry mouth occurs almost universally, particularly so with amitriptyline. In fact it is sometimes said that if a patient does not develop a dry mouth he should be suspected of not taking the drug. Dryness of the mouth is sometimes accompanied by intense thirst, an unpleasant taste, a dirty or black tongue, or small superficial ulceration of the buccal mucosa. Rarely a monilial infection (thrush) may supervene. There is no means of combating dryness of the mouth except by sucking fruit gums and other simple measures.

Constipation is usual although occasionally a patient may experience diarrhoea. Mild laxatives may be required.

Hesitancy of micturition is particularly liable to worry elderly patients and may occasionally result in retention of urine. Catheterisation may then be necessary. Patients with difficulties of micturition, due perhaps to prostatic hypertrophy, are particularly liable to be affected. Much less common is frequency of micturition.

Sweating is sometimes profuse, and occurs particularly over the head and upper half of the body and at night. It may be accompanied by flushing of the face.

Faintness or dizziness, most marked when changing position, is due to postural hypotension. This may become both troublesome and dangerous, particularly in elderly patients, who may readily sustain fractures as a result of falling. The dosage must be reduced if this side effect becomes severe. Dextroamphetamine, 5 mg twice a day, may be helpful, but in most cases the beneficial effect is doubtful.

Orthostatic hypotension mainly occurs only in elderly or hypertensive patients and it is advisable to start treatment with a small dosage in such patients.

Drowsiness, light-headedness, and occasionally a sense of depersonalisation are common in the first week of treatment. These effects tend to disappear when the antidepressant activity of the drug starts to be felt. It is sensible to warn a patient of the possibility of these effects at the start of treatment, otherwise their occurrence may make him unwilling to continue the drug.

Blurring of vision and difficulties of visual accommodation occur, but lessen with time and are rarely troublesome. It is important to remember that glaucoma may be precipitated or exacerbated by the tricyclic compounds.

Tachycardia is a common effect. Rarely, and on a high dosage of 225–300 mg a day, this may be so extreme as to result in cardiac failure. Occasionally auricular fibrillation may occur[134], and will resolve within a week of stopping the drug. Myocardial infarction

following the taking of antidepressant drugs has been reported.

Neurological symptoms are common.

Tremulousness can vary from a vague sensation of restlessness and twitching to uncontrollable violent shivering. It is more likely to occur with imipramine than with its analogues. Dosage should be reduced, but if trembling continues it is advisable to change to a tricyclic analogue. It is as well to remember that when imipramine is given alone it is liable to increase anxiety and agitation, which may be confused with these side effects.

Difficulty in speaking, pains in limbs, and weakness of legs may also occur.

Epileptic fits occasionally occur with high dosage.

Paraesthesiae, mainly of a prickling or burning nature in the limbs, or an unpleasant cold feeling in the legs, are sometimes experienced.

Peripheral Neuritis has been reported to occur during treatment with amitriptyline[95], with full recovery after stopping the drug. This is probably a toxic hypersensitivity reaction.

Gastrointestinal symptoms, in addition to constipation, may be troublesome. Nausea and vomiting are uncommon, but it is quite frequent for patients to complain of an unpleasant burning sensation beneath the sternum or in the epigastrium, particularly while taking imipramine. A number of patients with a history of excessive alcohol intake have developed peptic ulcers while taking imipramine or amitriptyline. Some of these ulcers have perforated. Whether there is a relationship between the occurrence of gastric ulceration and tricyclic antidepressants requires confirmation. Contrary to this possibility is the suggestion that imipramine or amitriptyline might be useful in the treatment of peptic ulcer because of their ability to reduce gastric secretion.

Abdominal distension may occur and occasionally progress to paralytic ileus[67].

Excessive weight gain[7] can be troublesome, more so with amitriptyline than with imipramine. Not only does the drug cause a patient to feel excessively hungry, but it also appears to put on weight by affecting central weight regulating mechanisms.

Slight *oedema* of ankles and puffiness of face may occur, but rarely requires treatment.

Difficulty in sleeping may result if imipramine (not usually amitriptyline) is given too late at night.

Sexual function may occasionally be upset, although it is sometimes difficult to assess how much this symptom is actually the effect of the drug and not the result of the illness. Impotence is unusual but delay in ejaculation can occur during the first few weeks of treatment[72].

Psychiatric complications can be troublesome, particularly in elderly patients and alcoholics. Imipramine and its analogues may

produce an acute toxic confusional state especially in the aged[108]. The risk of this is increased by the presence of other drugs, especially anti-Parkinsonism drugs. Visual hallucinations are particularly vivid and frightening[105]. These reactions are best treated by reducing or stopping the drug and giving chlorpromazine 150–300 mg a day.

Depression may give way to mania in a predisposed individual. In a severe manic state it is sensible to stop the antidepressant and substitute large doses of chlorpromazine and haloperidol or lithium carbonate. But in hypomanic states, particularly if the patient is already receiving amitriptyline, it is usually enough to reduce the dose of amitriptyline and add chlorpromazine or lithium carbonate.

Schizophrenic symptoms may also be brought out or exacerbated. The antidepressant drug should be stopped and the dosage of the phenothiazine drug increased until symptoms are controlled.

Toxic hypersensitivity effects include jaundice, skin reactions and blood changes, similar to those which may occur after chlorpromazine.

Jaundice is of the obstructive type, is rare, and is reversible on stopping the drug[85]. It is safe to change to another of the tricyclic compounds after jaundice has resolved.

Skin reactions, which are also unusual, include urticaria, angioneurotic oedema, and photosensitivity. Pruritus may be troublesome. These reactions generally disappear within a week of withdrawing the drug.

Blood changes are rarely important. Eosiniphilia is not uncommon and is of no consequence. White cells tend to fluctuate both in absolute numbers and in relative proportions. Agranulocytosis is very rare, but can occur[5,68].

OVERDOSAGE

The available estimates suggest that the lethal dose of imipramine is 2·5 g. Loo and his colleagues[121] report the successful suicide of a woman of 33 who ingested this dose.

(*b*) *Desipramine* (*Pertofran*)

It has been suggested that the antidepressant effects of imipramine are not caused by the drug itself but by one of its metabolites, and that delay between giving the drug and signs of clinical response is due to the time taken for an effective concentration of the metabolite to build up at the site of action. Various breakdown products of imipramine have been studied, one such being desipramine which is formed by removing one methyl group from the side chain nitrogen of imipramine.

Animal experiments show desipramine to possess a more rapid and powerful action than imipramine. But the results of recent

clinical trials on humans have not been particularly encouraging, although earlier uncontrolled trials claimed to find the antidepressant effects of desipramine quicker than and equal or even superior to that of imipramine. Desipramine is in fact probably a less effective antidepressant than imipramine, and does not appear to be the active metabolite of imipramine[59].

Side effects are similar to those of imipramine.

Dosage is similar to that of imipramine, 150–300 mg a day in three divided doses.

(c) *Amitriptyline* (*Tryptizol, Laroxyl*)

Amitriptyline has been in use clinically since 1961. It is not a MAO inhibitor and in structure it resembles imipramine and chlorpromazine. It is rapidly metabolised in the body in a manner similar to the breakdown of imipramine.

Amitriptyline, like imipramine, has a wide variety of pharmacological actions. It possesses strong anticholinergic (atropine-like) and antihistaminic properties and weak anti-serotonin actions. Its side effects therefore resemble those of imipramine.

Clinically amitriptyline has similarities to the actions of both imipramine and chlorpromazine. Not only does the drug possess antidepressant properties but, unlike imipramine, *it also alleviates anxiety and agitation.*

CLINICAL EFFECTS

Amitriptyline is clinically most effective in milder forms of endogenous depression accompanied by anxiety or agitation. In these conditions it is generally superior to imipramine, even when the latter is combined with a tranquilliser.

Like imipramine, antidepressant effects may not appear for a week or more after starting treatment. But the drug's sedative properties make themselves felt immediately, a fact to be welcomed when agitation or anxiety are severe. Less anxious patients are sometimes upset by the excessive tiredness and sleepiness which often occur during the first four or five days on the drug. These effects can be minimised by starting with a small dose, 75 mg a day, and working up to the full dose of 150–225 mg a day, over a week. They will also be lessened if a large part of the daily dose, 75–100 mg, is given at bedtime. Since insomnia, both initial and late, is frequently a symptom of agitated depression, this procedure has a double advantage. After about a week, when the drug's antidepressant effects begin to be felt, the heavy sedative effect lessens or disappears and is replaced by a sense of calmness. Sleep and appetite improve and there is often a considerable and sometimes excessive weight gain.

Like imipramine, amitriptyline merely suppresses symptoms and

must therefore be continued until the depressive illness resolves itself. The same procedure as with imipramine is adopted, the dose being slowly reduced every three months to find out if depression is still present, and immediately increased if symptoms recur. Some patients need to continue the drug for years. There is no evidence that this is harmful, and it is preferable to repeated courses of ECT or to enduring years of depression and suffering.

When anxiety or agitation are severe it is often advisable, in spite of amitriptyline's sedative properties, to combine the antidepressant with a tranquilliser.

L.J. is a man of 46, a perfectionist, energetic and able, always living at a high degree of tension. Fifteen years prior to being seen he had developed anxiety and depression following the break-up of his marriage. These symptoms had gradually resolved, without treatment, after one year.

When seen he was extremely agitated and feared that he had heart disease. He experienced palpitations, breathlessness and an unpleasant sensation over his heart. He was unable to get to sleep without a barbiturate, and he woke before dawn, sweating and worrying about his future. His powers of concentration, interest, energy and confidence were greatly diminished. He had lost just over 7 lb in the six months these symptoms had been present. He was not suicidal. He had been treated previously with trifluoperazine alone and then with phenelzine for one month without relief.

He refused to have ECT. He was therefore given amitriptyline 50 mg a day combined with trifluoperazine 1 mg, both three times a day. A week later he reported that his sense of agitation had virtually disappeared and that he was beginning to feel more cheerful and confident. After a month he said that he was back to his former state of health and felt neither abnormal anxiety nor depression.

Trifluoperazine was stopped and he was told to continue with amitriptyline alone. Anxiety symptoms began to recur and when seen a week later he was again agitated and concerned about the state of his heart. Depression had not returned however, a fact he remarked upon spontaneously, and he had been able to continue working with his usual efficiency. Resumption of trifluoperazine caused anxiety to disappear.

Four months later he was able to reduce and stop trifluoperazine, but it was a further six months before amitriptyline could be stopped.

In this case anxiety and depression once started, seemed to run almost independent courses, requiring independent treatment.

Amitriptyline is not as effective as imipramine in depressive states where retardation is more prominent than anxiety or agitation.

A woman of 72 had, for the past ten years, become depressed each year at the beginning of November. When depressed she slowed down noticeably, both physically and mentally, and was unable to make the simplest decision. Unless disturbed she would sit motionless for most

of the day staring at the floor. At the start of an attack she was given amitriptyline 225 mg a day for three weeks without improvement. On imipramine she showed signs of improvement after a fortnight, and of almost full recovery after six weeks. This sequence of events was repeated during the following year's depression.

As with all antidepressant drugs, ECT should never be withheld from severe states of depression, or when there is a risk of suicide. Amitriptyline may be safely combined with ECT and, provided it has been given for at least a fortnight beforehand, may reduce the number of shocks required. Even though response to ECT may appear to be complete, it is advisable to guard against the possibility of relapse by continuing the drug in full dosage for at least three months after depressive symptoms have disappeared.

Amitriptyline is a safer drug than imipramine or the MAO inhibitors to give to schizophrenic patients who become depressed after treatment. The risk of bringing out or exacerbating schizophrenic symptoms is small. It is best to give a small dose initially, say 10–25 mg twice or three times a day, and increase over a week to 150 mg a day. This procedure minimises the unpleasant tiredness that may occur at the start of treatment with amitriptyline, and which may prove as intolerable to some schizophrenic patients as to patients with reactive depressive illness. If schizophrenic excitement or other psychotic signs should increase during treatment with amitriptyline it is usually sufficient to increase the dosage of the appropriate phenothiazine compound.

R.S., at the age of 24, developed symptoms of acute schizophrenia requiring admission to hospital. Symptoms were controlled by means of ECT and phenothiazine derivatives. He was sent home after six weeks on a maintenance dose of trifluoperazine 20 mg a day and orphenadrine.

He became increasingly depressed and disinterested in his surroundings. Eventually he was given amitriptyline 150 mg a day; after 3 weeks was considerably brighter. Two months later he began again to develop ideas of reference and to notice "double meanings" in what people said to him or in what he overheard. Amitriptyline was continued in the same dosage, but trifluoperazine was increased to 30 mg a day and chlorpromazine 100 mg was given at night. The psychotic symptoms disappeared rapidly and over the course of the next six weeks it was possible to reduce the drugs to the initial dosage.

Amitriptyline is a useful drug in the management of "mixed manic-depressive" states and in states of mania and hypomania. This may seem paradoxical in view of the fact that hypomania can occur during treatment with amitriptyline. However, the drug appears to stabilise mood, having the effect of raising or lowering mood as required towards normality. In cases of mild mood fluctuations, amitriptyline alone may be sufficient. When larger swings occur

the addition of lithium carbonate or haloperidol will help to control mania, and of isocarboxazid to control depression.

F. suffered from manic depression, as a result of which he oscillated rapidly between mania and severe depression. Admission to hospital had been required for both states in the past. ECT had sometimes, but not invariably, helped to lift depression. Continuous narcosis or heavy sedation and large amounts of chlorpromazine had been required to control mania.

For the past two years he has taken a maintenance dose of 100 mg a day of amitriptyline. When depression begins to manifest itself he adds isocarboxazid 30 mg a day, and if necessary increases the dose of amitriptyline to 150 mg a day. When he starts to become over-active and to show signs of hypomania, he adds lithium carbonate 0·75 g a day. Once symptoms, depressive or hypomanic, are controlled he slowly reverts to the maintenance dose of amitriptyline alone.

Amitriptyline's sedative qualities, and its ability to potentiate the effects of barbiturates, make it a valuable drug in the treatment of initial insomnia, particularly when this is a symptom of a chronic tension-depressive state.

A man of 34 had had difficulty in getting to sleep since his undergraduate days. He felt tired on going to bed, but as soon as he lay down his mind became active and filled with worrying thoughts. If it was several hours before he got to sleep he always awoke feeling exhausted, with a pressure type of headache which persisted throughout the morning. He had tried a wide variety of hypnotics. When first seen he was taking 540 mg (9 gr) tuinal and three 650 mg tablets of dichloralphenazone (Welldorm) on retiring.

He was given 75 mg of amitriptyline and 200 mg tuinal. He began to sleep more soundly and to awaken feeling refreshed and clear-headed.

Amitriptyline can also be used in the treatment of nocturnal enuresis (see p. 51).

DOSAGE

The average daily dosage found to be effective is 150 mg. The minimum dosage necessary to achieve improvement in depressive illness is about 75 mg a day. Occasionally a patient will fail to respond to the drug until the dosage is increased to 225–300 mg a day. There is probably no advantage in going beyond this dosage and side effects will become marked.

TRIALS

As so often, the spate of reports of uncontrolled trials does not give much helpful information, with the exception of one by Ayd[10]. In a trial of 130 depressed patients he found that when improvement occurred it did so soon after starting treatment, and that the best results took place in manic depression and involutional (agitated) depression.

The view of many clinicians is expressed by Forrest[65] and by Skarbek and Smedberg[176], that amitriptyline has greater sedating qualities than imipramine but is a less effective antidepressant.

Hordern[92] on the other hand, in a blind controlled trial, found amitriptyline to be significantly superior to imipramine in the treatment of hospitalised depressed female patients aged between 30–70 years of age. Linford Rees and Davis[159] carried out a double-blind controlled trial of amitriptyline on twenty-seven depressed in-patients. They found that, like other antidepressant drugs, amitriptyline was of limited value and was unable to replace ECT.

COMBINATIONS OF AMITRIPTYLINE AND OTHER DRUGS

Amitriptyline and ECT. For this there is no contra-indication. If amitriptyline is started at least a fortnight before ECT is given the number of treatments required may be lessened.

Amitriptyline and tranquillisers or sedatives. Amitriptyline itself has tranquillising properties and may potentiate the effects of a tranquilliser. Paralytic ileus, for instance, may result from combining amitriptyline and chlorpromazine. But in general there are no contra-indications to combining amitriptyline with a tranquilliser or sedative. There has been a single report of bizarre symptoms developing in a patient receiving amitriptyline and chlordiazepoxide.

It is desirable to combine a tranquilliser such as trifluoperazine, 3–6 mg a day, with amitriptyline when treating a severely agitated patient. And amitriptyline combined with a phenothiazine compound may prevent depression developing in a schizophrenic patient. When insomnia is a prominent symptom, amitriptyline 50–75 mg given at bedtime with a hypnotic and, if need be, chlorpromazine 50–100 mg, will prove to be a highly effective combination.

Amphetamine if given in combination with amitriptyline may reduce the sleepiness and muzziness which sometimes occur during the first week of treatment.

Amitriptyline and other antidepressant drugs The risks and advantages of combining amitriptyline with a MAO inhibitor are discussed fully on page 52.

(*d*) *Nortriptyline* (*Aventyl, Allegron*)

Nortriptyline is the demethylated metabolite of amitriptyline. It was introduced for clinical use in 1963.

Clinical. Like amitriptyline, nortriptyline appears to be an effective antidepressant drug in cases of *mild* depression accompanied by tension. The drug has stronger sedating effects than amitriptyline and seems to be particularly useful when somatic symptoms, the result of tension, predominate.

Mrs. T., aged 36, had suffered from migraine since puberty. Over the

past three years headache had become almost continuous. She felt tired, irritable, and continuously ill, and was barely able to keep her home going. She had difficulty in getting to sleep without a hypnotic, and was liable to waken several times during the night. Headache was usually present on wakening and increased as the day went on. She had only lost a few pounds in weight. Repeated investigations failed to disclose any physical abnormality.

She was at first given phenelzine and perphenazine, but felt muzzy and even more unwell on these drugs. Tranylcypromine also upset her and increased tension. Amitriptyline caused her to feel extremely sleepy and she refused to continue the drug. ECT was considered, but it was decided first to try the effect of nortriptyline. She was given 10 mg three times a day, and 25 mg at night. When seen a fortnight later she looked and reported that she felt much brighter, less tense, and more able to cope with her responsibilities. Headache was not so troublesome and was becoming less frequent. She continued to improve. An attempt to stop the daytime dose of nortriptyline after three months resulted in a temporary return of symptoms.

Trials. Reports of uncontrolled trials with nortriptyline give the usual 70–80 per cent improvement rates in depressive illness.

Few controlled trials have been reported. Forrest[65] compared the effects of nortriptyline and amitriptyline in a group of mildly depressed patients. The drugs were given for between fourteen and eighteen days and the dosage of nortriptyline given varied from 30–150 mg a day. He found nortriptyline to be better than amitriptyline, although not significantly so. Rose[162], in a single blind trial of nortriptyline and amitriptyline, was another who found no significant difference in outcome, although amitriptyline appeared to be consistently more effective. This trial lasted four weeks and patients with severe depression were not excluded.

Dosage. Sedative effects may be troublesome and it is advisable to start with a smallish dose, 10 mg three times a day, 25 mg at night. This can be increased if necessary to 25 mg four times a day. It is rarely necessary or advisable to exceed a total dosage of 150 mg a day.

Side and toxic effects resemble those of imipramine and amitriptyline. Dryness of mouth, vertigo, constipation, termor, sleepiness and excessive sweating are the most common symptoms. Auditory and visual hallucinations occasionally occur, particularly in the older age groups.

Combined antidepressant therapy, giving nortriptyline with a hydrazine MAO inhibitor, is probably as safe as with amitriptyline.

(*e*) *Opipramol* (*Insidon*)

Opipramol is a compound belonging to the iminodibenzyl family. Its nucleus is almost identical to that of imipramine, while its side chain is identical to that of perphenazine.

The drug is claimed to be particularly useful in mild depressive conditions accompanied by tension and anxiety. In practice sedating properties are more apparent than antidepressant activity. The results of a controlled trial[71] of opipramol and chlordiazepoxide in anxiety states suggested that both drugs were equally effective in relieving anxiety. The dosage is 50–100 mg three times a day.

Side effects are of sleepiness, tiredness, nausea, giddiness, dry mouth and blurred vision.

(*f*) *Trimipramine* (*Surmontil*)

This tricyclic antidepressant has become available for clinical use comparatively recently. It resembles imipramine in structure, the difference lying in an extra methyl group attached to the central carbon atom of the side chain of trimipramine.

Clinical. It seems that, like imipramine, trimipramine is most effective in endogenous forms of depression. It has greater sedative properties than imipramine but it is usually advisable to combine a tranquilliser such as trifluoperazine with it in cases characterised by much anxiety.

Few satisfactory controlled trials have yet been reported and, as usual, the results are ambiguous.

Dosage. It is advisable, because initial sedating effects may be marked, to begin treatment with 75 mg a day in three divided doses, the last being taken at bedtime. The average effective dose is between 150–300 mg a day. There is a delay of 7–14 days between starting the drug and the appearance of antidepressant effects.

Parenteral injection is rarely required unless the patient is uncooperative, when ECT is usually advisable. The dose is 25–50 mg three or four times a day.

Side effects are similar to those caused by imipramine. Sleepiness may be troublesome initially. Care is required when treating elderly or arteriosclerotic patients because, like other tricyclic antidepressants, the drug may cause a confusional state. Hypomania, convulsions and rarely extrapyramidal side effects occur when very large doses are given.

Overdosage results in hypotension, convulsions and coma. Treatment must be based on symptomatic relief.

CHAPTER III

DEPRESSANT DRUGS—I

TRANQUILLISERS WHICH CAUSE EXTRAPYRAMIDAL SIDE EFFECTS

THE PHENOTHIAZINE DERIVATIVES

Phenothiazine was introduced over fifty years ago as an anthelmintic for livestock, as a urinary antiseptic in man and as an antihistaminic. But phenothiazine proved to be too toxic in its effects for clinical use and interest in the compound lapsed for a time. Interest revived after the last war, because of search for new and better antihistamines, and the phenothiazine derivatives were developed. Pharmacologically phenothiazine derivatives depress the central nervous system (CNS). Peripherally, and by inference centrally, they have anti-adrenergic and anti-cholinergic effects.

Promethazine (Phenergan) was the first of these derivatives to be used clinically, and is still in use today both as an antihistamine and as a tranquilliser and a hypnotic. Chlorpromazine was introduced in 1951 and was found to have a wide variety of actions, particularly in the treatment of psychotic conditions. Since then, by chemical substitution in two positions, R1 and R2, many new phenothiazine derivatives have been introduced.

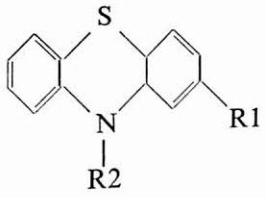


Figure 1
Phenothiazine nucleus

All the phenothiazine derivatives are tranquillisers, in that they sedate and calm without causing undue sleepiness or impairing consciousness. In varying degrees they reduce motor activity and aggressive behaviour, influence the endocrine and autonomic nervous systems, exert antihistamine effects and intensify and prolong the

depressant activity of barbiturates, alcohol and narcotic analgesics. Some, especially the piperazine phenothiazines, have pronounced effects upon the extrapyramidal system. These effects may be due either to reduced adrenergic activity, or to cholinergic activity in the extrapyramidal system, since they are reduced by centrally active anti-cholinergics.

According to the substituent at R2, the phenothiazines can be classified into three groups:

(1) A dimethylaminopropyl side chain, such as promethazine (Phenergan), promazine (Sparine), and chlorpromazine (Largactil).

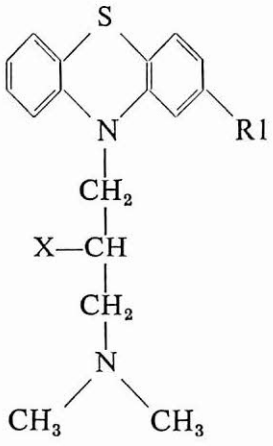


Figure 2
The 2-substituted-10-(3-dimethylaminopropyl)-phenothiazines

(2) A piperidine side chain, such as mepazine (Pacatal) and thioridazine (Melleril).

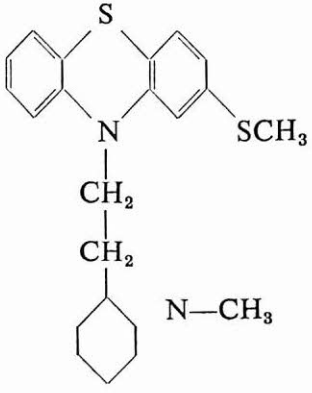


Figure 3
Thioridazine

(3) A piperazine side chain such as trifluoperazine (Stelazine).

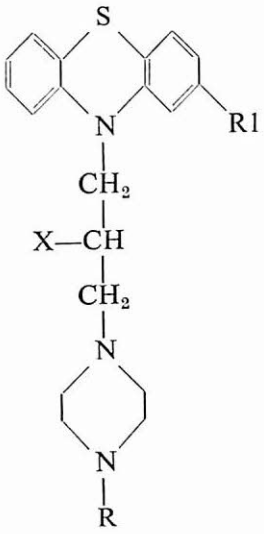


Figure 4
The 2-substituted-10-(3-piperazinopropyl)-phenothiazines

The most marked effects on the central nervous system occur when the chain at R2 includes three carbon atoms in a row, and all the phenothiazine derivatives which are effective in controlling psychotic symptoms contain this.

Substitution also occurs at R1, usually replacing the hydrogen atom either by chlorine or fluorine. R1 and R2 substitutions both alter the clinical effectiveness and side effects of the drug. The presence of fluorine at R1 particularly seems to increase the incidence of extrapyramidal side effects.

The main clinical uses of the phenothiazine derivatives are:

(*a*) In psychiatry, to control psychotic illness and abnormally disturbed behaviour.
(*b*) As an anti-emetic.
(*c*) In anaesthesia and hypothermia.
(*d*) To potentiate sedatives, hypnotics and analgesics.
(*e*) To control a variety of conditions such as hiccough, and pruritus.

CHLORPROMAZINE (LARGACTIL)

Delay and Deniker[54] in 1952 reported that chlorpromazine was effective in the treatment of certain psychotic disorders, would dispel delusions and hallucinations and control overactive states. Their

results were confirmed by later investigators and from 1954 onwards chlorpromazine began to be used increasingly in psychiatry.

Chlorpromazine is most effective in controlling disturbed psychotic patients who may be excited or agitated, and in suppressing delusions and hallucinations. The drug relieves or suppresses symptoms. It does not cure or have a direct action against specific psychiatric conditions. None of the phenothiazine derivatives has any specific antipsychotic action, but in many instances they are able to arrest the progress of psychotic disorders which, if allowed to continue, would lead to further impairment of the patient's contact with reality. They interrupt a vicious circle and allow the patient's CNS to function in a more normal manner. Thus, chlorpromazine is valuable in the treatment of disturbed schizophrenics, of patients with agitated depression or mania, hyperactive subnormal individuals, confusional states, and conditions such as anorexia nervosa where the patient is likely to be obstructive and try to resist treatment.

TREATMENT OF SCHIZOPHRENIA

The value of chlorpromazine in the treatment of schizophrenia was quickly recognised. Within a few years of its introduction chlorpromazine had almost entirely replaced deep insulin therapy as the standard treatment of schizophrenia, although some authorities still maintain that insulin therapy produces a fuller and longer lasting remission than the phenothiazine derivatives do[185].

It is generally believed that insulin therapy, when given in the first year of illness, doubles the remission rate[3], but has little effect on the course of the disease if given later. Few controlled trials have been conducted. Authorities such as Langfeldt[112] long ago pointed out that patients who recovered after treatment with insulin seemed in the main to have what he called "schizophreniform psychoses," with a high spontaneous remission rate, rather than true or nuclear schizophrenic illnesses.

Reliable comparison of the results of treatment with phenothiazines and insulin is difficult to assess, and is made more so by the fact that there appears to have been a steady improvement in the prognosis of schizophrenia[197] throughout this century (probably due to changing social attitudes). However, it seems unlikely that the results of treatment with chlorpromazine are inferior to those achieved with deep insulin therapy.

Chlorpromazine is an easier and less dangerous form of treatment than deep insulin therapy. It is probably superior in the treatment of schizophrenia which has lasted for more than a year, and in the treatment of and prevention of relapse.

Chlorpromazine is particularly useful in the treatment of agitated, fearful, deluded and hallucinated patients, and those who are over-

active, violent and difficult to control. It is more effective in patients whose affect is still intact, and in whom schizophrenic symptoms have developed acutely and suddenly, either for the first time or in relapse. The drug is less effective in the treatment of anergic and withdrawn patients who show emotional poverty, and where the illness has developed slowly and insidiously over a long time. Nor is chlorpromazine helpful in the type of case sometimes unfortunately labelled "pseudoneurotic schizophrenia". Patients with paranoid schizophrenia are often helped by a phenothiazine, with relief of anxiety and depression, although the paranoid delusion is all too often unaffected by treatment. This is particularly so in the older age groups and in those patients with well-preserved personalities.

It is the emotional rather than the intellectual aspects of the patients' illness which are influenced by phenothiazines. Acute schizophrenic symptoms may disappear rapidly within a week or fortnight of starting treatment. Psychotic agitation and anxiety are usually the first symptoms to disappear. Without their accompanying affect, delusional ideas and hallucinations tend to lose their hold, cease to preoccupy and influence the patient's thinking and may fade or disappear altogether. Thinking gradually becomes more orderly and emotional responses cease to be inappropriate and incongruous. As the patient begins to return to normality it becomes possible to communicate more rationally with him and to establish a therapeutically useful relationship.

H.G. was in his last year at University, reading history. Towards the end of the Easter term he became increasingly excitable and strange in his behaviour. He noticed that newspaper reports, a television programme, and the remarks of strangers in the street contained double meanings which warned him of impending danger. He was convinced that he was being followed and watched. His state of excitement mounted and eventually he began to hear a voice, warning him that some sort of time-bomb was hidden in the furniture of his room. He began ripping up the furniture and throwing it out of the window. He made a violent assault on a porter who tried to remonstrate with him, and eventually the police had to be summoned.

He was quietened with injections intramuscularly of chlorpromazine 100 mg and paraldehyde 15 c.c. Subsequently he was given chlorpromazine 800 mg a day in four divided doses by mouth. After ten days he had lost all his symptoms. The dosage of chlorpromazine was reduced progressively to 300 mg a day and he was discharged on this dose after three weeks.

It is important to gain the patient's co-operation as quickly as possible, and to reinforce and follow up the improvement brought about by chlorpromazine by means of psychotherapy, occupational therapy and general methods of resocialisation. Chlorpromazine should always be combined with these other forms of therapy;

its effectiveness is considerably diminished when used on its own.

Although a more liberal attitude towards patients was beginning to permeate mental hospitals before the advent of the phenothiazine derivatives, there is little doubt that the ability of these drugs to control disturbed behaviour has helped to speed up this trend. Fewer wards now need to be locked, patients can be given more freedom and personal responsibility, and resocialisation is thereby made easier.

If a patient is disturbed and difficult to control even with large amounts of chlorpromazine, or if improvement is slow, ECT should also be given.

> R.S., aged 22, an architectural student, developed psychotic symptoms after an unsuccessful love affair. He felt that he was changing his sex and was convinced that his father was in some way responsible. He was hallucinated and his behaviour alternated between extreme excitement and elation and semi-stupor. He was admitted to hospital and treated with chlorpromazine, the dosage of which was increased steadily from 600 mg to 1000 mg a day. His behaviour became more manageable but delusions and thought disorder remained after a fortnight. 8 ECT were now given (three a week), and after the fifth treatment there was a very marked improvement. After six weeks he was sent home, symptom-free, on a maintenance dose of chlorpromazine 300 mg a day.

ECT alone has little or no lasting effect in the treatment of schizophrenia,* although it is often very useful in relieving catatonic and depressive symptoms. However, giving ECT with chlorpromazine or another phenothiazine does render the patient more accessible and easier to manage (an important factor if the patient is receiving treatment in a general hospital), and seems to speed up the rate of recovery[101]. Generally 8–12 treatments are given but each case needs to be assessed individually.

It is difficult to say whether this combined chlorpromazine and ECT treatment induces a fuller or better improvement than chlorpromazine alone, for no adequate trials have been made. But it does appear to shorten the time the patient spends in hospital. For instance, the average time spent in hospital by first admission schizophrenic patients who were treated immediately with a phenothiazine and ECT was thirty-three days, compared to an average of forty-two days by comparable patients treated with a phenothiazine alone (see Table VI). The clinical state of both groups on discharge was similar.

The nutritional state of schizophrenic patients on admission to hospital is often poor. It is important, at the same time as pheno-

* Authorities such as Langfeldt[112] consider that those patients who recover after ECT alone have a "schizophreniform psychosis" rather than "true" schizophrenia.

thiazine treatment is given, to correct nutritional deficiences and to restore lost body weight. Treatment with large amounts of chlorpromazine will often induce considerable weight gains, not entirely due to increased appetite. But when weight loss has been considerable, or restoration of weight is slow, the use of modified insulin as well may be helpful in increasing the patient's hunger and desire to eat (see also p. 80).

Other forms of adjuvant drug therapy may be required, including antiParkinsonian drugs, antidepressants and other tranquillisers. (See Table VI.) Their use in combination with chlorpromazine is discussed below.

TABLE VI

Treatment of schizophrenia in the Psychiatric Unit of Westminster Hospital

	1st admissions (*46*)	*2nd or more admissions* (*32*)
Treated with a phenothiazine derivative alone	5	9
ECT also given		
(*a*) Total number of patients	41	23
(*b*) Started within a week of admission	28	21
Average number of ECT given	9	7
Antidepressant drugs given during treatment	13	7

Chlorpromazine is unable to help the majority of chronic schizophrenic patients. Apathy and emotional blunting, loss of drive and inertness are not improved by chlorpromazine, and occasionally may even be increased due to the drug's sedative effect. Phenothiazine derivatives carrying a piperazine side chain have less of a sedating effect and therefore are often better than chlorpromazine in the treatment of deteriorated or "inert" schizophrenic patients (see trifluoperazine, below).

TRIFLUOPERAZINE (STELAZINE)

Weight for weight, trifluoperazine is more potent than chlorpromazine, so that dosage is smaller. However, from a clinical and therapeutic point of view this is of no importance and side effects, particularly extrapyramidal, from 30 mg of trifluoperazine a day may be as troublesome as from 800 mg chlorpromazine.

Trifluoperazine exerts broadly similar effects to chlorpromazine,

but is less sedating and more stimulating. Indeed its stimulating effects may bring about too great a degree of tension in some psychotic patients. However, this property makes trifluoperazine, and other piperazine phenothiazines, particularly useful in the treatment of anergic withdrawn schizophrenic patients. As with chlorpromazine, abnormal affect and thinking may be improved, and in addition the patient will show more drive and alertness. The stimulating effect of trifluoperazine is also reflected in mood lift, which makes it a better drug than chlorpromazine to use when depression is also present.

Paranoid schizophrenia may also respond better to a piperazine phenothiazine than to chlorpromazine, particularly when, as so often is the case, depressive symptoms are present.

Some authorities recommend combining chlorpromazine with a piperazine phenothiazine in treatment-resistant schizophrenics, but there is little evidence that such a combination has advantages over treatment in adequate dosage with a single phenothiazine. But when a disturbed schizophrenic patient is controlled by chlorpromazine, it is sometimes advantageous to change over gradually to trifluoperazine, either because of undesirable side effects, or because chlorpromazine is causing tiredness and depression of mood. Conversely, if the piperazine phenothiazine overstimulates and causes an undesirable degree of tension, it may be desirable to change to chlorpromazine or thioridazine. During the change over it is best to overlap the two drugs concerned, progressively reducing or increasing the dosage of each.

Ursula, 19, became withdrawn and depressed and was unable to concentrate on her work. She was admitted for observation, was diagnosed as having schizophrenia, and was started on trifluoperazine, 10 mg three times a day together with orphenadrine. She became increasingly restless and tense and after three days developed auditory hallucinations. Chlorpromazine 100 mg three times a day was given and increased by 150 mg a day to a daily dosage of 800 mg. At the same time trifluoperazine was reduced by 5 mg a day and stopped after six days. Anxiety and restlessness progressively diminished and after a week on chlorpromazine alone she was no longer hallucinated.

MAINTENANCE TREATMENT WITH PHENOTHIAZINE DERIVATIVES

The phenothiazines suppress and control symptoms. They do not cure. Long term maintenance treatment with the appropriate phenothiazine is therefore of great importance in preventing relapse.

Within one year of having been discharged back to the community from London mental hospitals, 55 per cent of a large group of schizophrenic patients showed signs of relapse and 43 per cent of them required re-admission[35,131,145,196]. Although the majority were discharged on a maintenance dose of a phenothiazine, half the

patients failed to take them as prescribed. And although the proportion of patients who attended aftercare clinics was high in the first month, attendance declined steeply in subsequent months and medical supervision and treatment lapsed.

It is the regular taking of a phenothiazine which prevents relapse. Medical supervision and support alone are of limited value. An American study[146] of schizophrenic patients recently discharged from hospital illustrates this point. The patients were assigned randomly to one of three groups: (1) regular medical supervision plus taking phenothiazines, (2) regular medical supervision plus a placebo, and (3) no particular supervision or drug therapy. There was a high rate of relapse in the last untreated group. The first and second groups did extremely and equally well for the first six months. But subsequently the phenothiazine treated group did better and after eighteen months 83 per cent of this first group remained in the community compared to 55 per cent of the second placebo treated group.

Although the regular taking of a phenothiazine is of prime importance in preventing relapse, regular medical supervision and support are of the greatest value in persuading the patient to continue his phenothiazine medication. For instance, while 25 per cent of schizophrenic patients followed up after discharge from hospital required re-admission within a year, 45 per cent of those not followed up needed to be re-admitted[141].

Particularly in London, the main responsibility for the day to day care of discharged schizophrenic patients falls on their general practitioner, some of whom are still unaware of the importance for these patients of continuing to take large amounts of phenothiazine drugs, for years if necessary.

> H. had developed schizophrenia three years ago, at the age of 26. At that time he had been treated in hospital for seven weeks with chlorpromazine, up to 800 mg a day, and ECT. His acute symptoms faded, delusions and hallucinations disappeared, and superficially he appeared to be fully recovered. However his former drive and energy failed to return and he admitted to having occasional bizarre ideas and to misinterpreting other people's remarks. After leaving hospital he continued to take 150 mg chlorpromazine a day (100 mg at night, 50 mg in the mornings) and on this dosage symptoms remained in abeyance. However, he had to move his home and as a result came under a new general practitioner. He was told to stop chlorpromazine and take phenobarbitone instead. A month later he was admitted under certificate, in an acutely disturbed schizophrenic state. This time he was in hospital for eleven weeks and was still far from recovered on discharge.

In practice most schizophrenic patients are told on leaving hospital that they *must* continue to take a phenothiazine drug for two years, or longer if any symptoms are still in evidence. Sometimes delusions or hallucinations may continue in spite of regular phenothiazine

medication, but they now no longer arouse strong emotions and the patient is able to tolerate them and to live within society.

Mrs. F. developed a hebephrenic type of schizophrenia shortly after her marriage at 19. Auditory hallucinations caused alternating moods of panic and anger. A prolonged course of deep insulin therapy accompanied by ECT failed to improve her and she spent the next twelve years in a mental hospital in a disturbed, unpredictable state. Then chlorpromazine was introduced and given to Mrs. F. There was a dramatic and rapid improvement in her mood and behaviour. Now, although she still heard voices making unpleasant remarks about her she was no longer upset by them. She was able to ignore her symptoms and for the first time for twelve years, to mix comfortably with other people. She was able to return home. She has continued to take 150 mg daily of chlorpromazine, temporarily raising the dose herself to 300 mg daily if symptoms increase or she feels mentally unwell. On one occasion when she ran short of chlorpromazine she rapidly relapsed and required 400 mg chlorpromazine daily for several weeks and ECT (given as an out-patient) before control could be regained.

There are occasions when a phenothiazine derivative is given prophylactically. Childbirth is a particularly dangerous time for a patient who has had a previous schizophrenic illness, particularly if this was precipitated by childbirth. Even though the patient may have made a full recovery it is often a wise precaution to give say 150 mg chlorpromazine daily during the last fortnight of pregnancy and continue this for the first month of the puerperium. Breast feeding is then best avoided. If, at the end of a month, there are no signs of relapse the drug can be reduced and stopped. But any signs or symptoms of schizophrenia necessitate prolonged phenothiazine therapy.

DOSAGE

Dosage varies within somewhat narrow limits between one patient and another. In general, the dosage is raised as quickly as possible until all symptoms are suppressed and then slowly reduced to a minimum which will prevent the emergence of symptoms.

The usual starting dose of chlorpromazine in the treatment of schizophrenia is 300 mg a day, given in three divided doses (see Table VII for dosage of other phenothiazines). This dosage is progressively increased by 150–300 mg daily, up to a maximum of about 1500 mg a day, until symptoms and disturbed behaviour are controlled. In the U.S.A. up to 4000 mg of chlorpromazine a day has been given, but there seems little to be gained therapeutically from the use of such a large dosage and side effects are troublesome. The average maximum daily dose needed is between 600–800 mg a day. Thereafter, once symptoms are controlled, the dosage is lowered slowly to the minimum required to control abnormal thought and

behaviour, usually not less than 150 mg daily. Any return of symptoms requires the dosage to be increased immediately.

At one time it was widely believed that the dosage of a phenothiazine derivative, to have maximum therapeutic effect, needed to be at such a level that extrapyramidal symptoms would inevitably appear. Most authorities no longer believe this and give anti-Parkinsonian drugs to avoid extrapyramidal side effects[18]. But others still hold to this early view[78] and avoid the use of anti-Parkinsonian drugs for this reason. However, extrapyramidal symptoms, particularly dystonia, can be both painful and frightening to the patient and may make him reluctant to continue treatment.

It has been assumed so far that the usual practice of giving divided doses of phenothiazine throughout the day, and so keeping the phenothiazine blood level constant, is the correct one. But some authorities have suggested that a single daily dose is sufficient, given say at night-time.

Delay[55] suggested that a *discontinuous* method of administering the phenothiazine might sometimes give better results and described such a procedure using thioproperazine. Five mg of the drug is given eight-hourly on the first day and increased by 5 mg a day until extrapyramidal effects appear. This dosage level is maintained for five days and is then stopped. Side effects usually disappear within the next two days and any improvement that is going to occur does so at this time. This procedure is then repeated starting with a dose just below the maximum dosage already found to be needed. The patient tends to become sensitive with time to the drug so that a smaller dosage will usually be needed next time. Up to six courses may be needed for maximum improvement. Subsequently, of course, the patient will require maintenance treatment.

Another form of discontinuous treatment consists of giving a daily maintenance dose of a phenothiazine and twice a week giving three or four times this dosage. Thus Boszormenyi[24] gives a daily maintenance dose of 30 mg methopromazine, and raises this twice a week to 90–120 mg, given in three divided doses during the day.

This treatment is looked upon as a form of chemical shock and claims have been made that it is sometimes more effective than continuous treatment in chronic anergic patients. Sudden collapse, with raised temperature and shock reactions, rarely resulting in death, is a complication of discontinuous therapy. It should be remembered however that similar reactions can also occur during continuous treatment.

The minimum dosage necessary to control symptoms is also the daily maintenance dose of chlorpromazine or other phenothiazine which the patient must be prepared to continue for at least two years after leaving hospital. In order to avoid undue sleepiness and interference with their working lives, some patients prefer to take the bulk

of chlorpromazine at night-time and a smaller dose in the morning; for instance on a maintenance dose of 150 mg a day, 100 mg at night and 50 mg in the morning. Others prefer to take the drug in three equally divided doses. It is better to adapt to individual preferences rather than work to a rule.

TABLE VII

Comparative dosage of phenothiazine derivatives in common use

	Neurotic and psychosomatic disorders		*Psychotic disorders*
Dimethylaminopropyl side chain			
Chlorpromazine (Largactil)	10–25 mg	twice or thrice a day	150–1500 mg a day
Promazine (Sparine)	25–100 mg	,,	*Not suitable
Methotrimeprazine (Veractil) (laevopromazine)	5–50 mg	,,	*Not suitable
Trifluopromazine (Vespral)	10–25 mg	,,	150–900 mg a day
Piperidine side chain			
Thioridazine (Melleril)	10–25 mg	,,	150–600 mg a day
Piperazine side chain			
Pericyazine (Neulactin)	5–10 mg	,,	30–200 mg a day
Trifluoperazine (Stelazine)	1–2 mg	,,	10–30 mg a day
Perphenazine (Fentazin)	2–4 mg	,,	24–72 mg a day
Prochlorperazine (Stemetil)	5–10 mg	,,	15–100 mg a day
Fluphenazine (Moditen)	1–3 mg	,,	15–300 mg a day
Thiopropazate (Dartalan)	5–15 mg	,,	150–450 mg a day
Thioproperazine (Majeptil)	Not suitable	—	30–90 mg a day

* Useful in alcoholic withdrawal states, in relieving the agitation of depressed patients, and in organic and senile confusional states.

Signs of relapse are an indication to increase the dosage of chlorpromazine at once to 300 mg a day or more until symptoms are once more under control. ECT may also be required and can be given, if necessary, on an out-patient or day hospital basis. If these steps are taken without delay, relapse can often be quickly reversed and re-admission to hospital prevented.

COMPARISON OF PHENOTHIAZINE DERIVATIVES

No marked differential therapeutic effects between the different phenothiazine compounds have been shown to exist[81], although individual patients will frequently respond better to one drug than another. Rough indications for when to give one or other type of phenothiazine exist and have already been discussed above. Much of the differences are probably due to the differential sedative effects and the liability of a drug to provoke side effects.

EFFECTIVENESS OF TREATMENT WITH PHENOTHIAZINES

The effectiveness of any treatment in schizophrenia is difficult to assess. Diagnostic concepts vary widely, so that it is often difficult or misleading to compare the results of one trial with another. It is sixty-seven years since Kraepelin differentiated *dementia praecox* from other psychoses, but from the time that Bleuler (1911) suggested replacing the term dementia praecox by schizophrenia, the boundaries defining the illness have steadily widened. Recently there have been attempts to return to the early Kraepelian concept of dementia praecox. Langfeldt[112] has tried to restrict the term schizophrenia to patients with a bad prognosis, suffering from *real* or *nuclear* schizophrenia. These patients, Langfeldt claims, are not basically improved by treatment. On the other hand less typical forms of schizophrenia, *schizophreniform psychoses*, which have a tendency to remit spontaneously, respond well to treatment. But it is not always possible, except in retrospect, to distinguish real schizophrenia from a schizophreniform psychosis. Terms such as pseudoneurotic schizophrenia[87], used fairly widely in the U.S.A., merely add confusion to a confusing subject.

Another difficulty in assessing the value of treatment is that there are no generally agreed criteria for assessing improvement. Various criteria are used: improvement in individual symptoms, the discharge rate, re-admission or relapse rates, the proportion of patients working or leading a "useful" existence. These criteria tend to measure different aspects of the results of treatment. And results will differ depending upon whether they are assessed from short or long term viewpoints.

The discharge rate from mental hospitals has been steadily increasing during this century. However it is generally agreed that treatment with phenothiazine derivatives has made possible the discharge of many more patients. Before 1939, nearly two-thirds of the schizophrenic patients admitted to a mental hospital would still be there two years later. Now less than 10 per cent of those admitted to hospital remain there after two years. The average length of stay of a patient in hospital can now be measured in weeks instead of years.

Kelly and Sargant[101] compared two similar groups of schizophrenics, one treated with deep insulin treatment, the other with phenothiazines, and found the phenothiazine treated group to be superior. Two years after discharge 93 per cent of these patients were in the community and 67 per cent of them fully independent.

That treatment with phenothiazines results in control rather than cure has been emphasized above. A high proportion of patients will relapse when their drugs are withdrawn, even after many years of treatment. Inevitably therefore the present high discharge rate is accompanied by high relapse and re-admission rates. This tendency is increased by the absence or inadequacy of long-term community care and support.

As with insulin therapy, phenothiazine treatment is most effective in cases of schizophrenia of relatively recent origin; recovery then tends to be fuller and quicker. Even so some of these patients do not respond well to treatment and steadily progress to chronic schizophrenia. Conversely, although the inert "silly" patient, lacking drive and affect, generally responds badly to treatment this is not always the case; occasionally such a patient will make a good recovery.

Every new case should be treated fully and enthusiastically for we are still unable to predict with certainty the outcome of any individual illness. Only in childhood schizophrenia can it be said with a fair degree of certainty that phenothiazine treatment is unlikely to improve the illness. But even here a phenothiazine drug may improve behaviour remarkably.

TREATMENT OF NON-SCHIZOPHRENIC STATES OF EXCITEMENT AND AGITATION

Phenothiazines, such as chlorpromazine or thioridazine, will reduce the restlessness and agitation which may occur in depressive illness, or in confusional states, and the excitement and overactivity of mania.

Depressive tension responds quickly to a phenothiazine derivative, but it is important to realise that none (with the exception perhaps of levomepromazine) has antidepressant effects. Severe agitation is best treated with chlorpromazine, but in milder cases not marked by restlessness a piperazine phenothiazine may be better. Dosage will depend upon the degree of agitation and what other treatment the patient is receiving. In relatively mild cases chlorpromazine 10–25 mg or trifluoperazine 1 mg, both three times a day, is given with an antidepressant drug, and is adequate. In addition, 50–100 mg of chlorpromazine at night taken with a hypnotic, ensures a sound night's sleep. More severe states of agitation, perhaps requiring in-patient treatment, will need larger doses.

Very severe depressive agitation may require *continuous narcosis* in addition to antidepressant therapy. Chlorpromazine has rendered this form of treatment safer than in the past when large amounts of barbiturates needed to be given. 600–800 mg of chlorpromazine a day is given in three or four divided doses, combined with sodium amylobarbitone 200–400 mg (3–6 gr.) three or four times a day or less depending on the depth of sleep and the patient's general state. It is best to give the drugs after meals as this allows the patient to be sufficiently wide awake at mealtimes to feed himself. Attention must be paid to fluid intake and output and at least 1500 c.c. of fluid a day drunk. Regular turning from side to side and, if possible, getting out of bed during the day, will help to prevent venous thrombosis,

hypostatic chest infection and lung collapse. During sleep, if necessary, ECT can be given.

Continuous or semi-continuous narcosis, given for up to 2–3 weeks and combined with antidepressant drugs, is often highly effective and will sometimes render ECT unnecessary. It is therefore a particularly useful procedure in patients who refuse to have ECT.

Acute confusional states occurring either during the course of a physical illness or as part of a dementing process will also respond well to chlorpromazine, given in doses of 150–300 mg a day. Chlorpromazine in such cases has considerable advantages over barbiturates, which may increase a patient's confusion and agitation. Delusions and illusions cease to terrify the patient or quickly fade, and the patient becomes accessible to reason and reassurance. In senile patients who may only become confused at night, 100 mg chlorpromazine at bedtime is usually enough to prevent agitation and to give a full night's rest.

Delirium tremens is still a difficult management problem with a mortality rate of about one in seven[118]. Chlorpromazine should be given as soon as possible and in adequate dosage. All too often the initial dosage given is far too small and the patient's condition rapidly deteriorates. Semi-continuous narcosis should be the aim and the dose of chlorpromazine with a barbiturate if necessary should be steadily stepped up until this is achieved.

Drug withdrawal states can also be treated satisfactorily by these means.

Manic overactivity is, in the initial stages of treatment, probably best controlled by large doses of chlorpromazine. In hypomania 100 mg of chlorpromazine at night may be sufficient to control symptoms, with or without 25–50 mg once or twice in the daytime. In severe mania up to 1000 mg of chlorpromazine a day may be needed. In some cases rapid control is achieved by giving the first few doses intravenously (50–100 mg) combined with intravenous amylobarbitone sodium 400 mg. If mania is acute haloperidol or thioproperazine can be given concomitantly.

Subsequently up to 800 mg chlorpromazine a day may need to be given. Chlorpromazine suppresses symptoms but does not cure the attack, and if the drug is stopped before the mania has spontaneously remitted symptoms will rapidly return. Depression may follow the manic episode and also require treatment.

Some patients with mixed manic depressive attacks respond best and can sometimes be stabilised on combined antidepressive and tranquillising drugs (see p. 51). A combination of amitriptyline 150 mg a day with chlorpromazine may be highly effective. Not only is

the combination effective in tranquillising the patient but it may prevent depression superseding mania.

Neurotic states of anxiety rarely benefit from chlorpromazine. Many such patients feel worse when given the drug, and complain of feeling tired, woolly-headed and even less able to cope with responsibilities than before.

Small doses of a piperazine phenothiazine are sometimes helpful, however, particularly for patients who develop anxiety symptoms in middle age or later without evidence of depression. Younger patients, and those with somewhat inadequate personalities, are not generally helped by phenothiazines and do better with a sedative or a tranquilliser such as chlordiazepoxide.

Patients with obsessional and compulsive states may also be upset and tend to feel depressed by chlorpromazine. Generally piperazine phenothiazines will not help uncomplicated obsessional and compulsive symptoms, unless these are being exacerbated by much anxiety.

R. had had obsessional and compulsive symptoms since puberty. He had to repeat certain words eight times, always had to open and shut several times the door of any room he entered, and went through certain grunting rituals at mealtimes. He lived with his mother and her lover. From time to time there would be scenes between the latter and the patient which always resulted in him becoming tense and anxious. At these times there would be a marked increase in his symptoms which would usually continue for several weeks. Perphenazine 2 mg three times a day would quickly reduce his symptoms to their normal level of activity.

Anorexia Nervosa was described by Gull[77] and Lasegue[114] nearly 100 years ago. The condition occurs mainly in young women who lose weight as a result of refusing to eat.

It is generally agreed that the refusal to eat and consequent weight loss, as well as amenorrhoea, is caused initially by psychological factors. The emaciated state which later develops is responsible for reinforcing and complicating the early symptoms.

Treatment falls into two separate but interrelated parts. Firstly, weight must be restored as quickly as possible. Menstruation will not return until weight is at least 75 per cent of "normal"[50]. Secondly, psychological conflicts need to be resolved and the patient supported psychotherapeutically until recovery is complete. This phase is often prolonged and difficult to manage. Refusal to eat may be replaced by compulsive over-eating and excessive weight increase, compulsive stealing and psychopathic behaviour. Alternatively, weight may be lost again and re-admission required. It is vital that the therapist should never give up hope with a case of anorexia nervosa.

Until these patients were treated with chlorpromazine, very often

combined with modified insulin[52], it was extremely difficult to persuade them to eat enough to regain weight. Mealtimes became a battleground, from which the patient not infrequently emerged victorious.

Patients almost invariably require to be admitted to hospital. They are put to bed at the start of treatment and told they must stay there until they regain a definite weight (dependent upon their age, height, body build and previous weight). Chlorpromazine is given by mouth, starting with 300 mg a day, and increased by 150 mg a day to the limit of tolerance. As much as 1600 mg a day has been needed in difficult patients. It is essential to increase the dose until the patient becomes virtually helpless. At this point she loses her ability to resist and ceases to feel panic at the sight of food or epigastric discomfort after eating. Modified insulin therapy is also begun at once, starting with ten units each morning one hour before breakfast and progressively increasing the dose until the patient sweats and becomes drowsy; the average dose for this is 40–60 units. Then interruption takes place with a large meal. Precautions are taken throughout the day to avoid occurrence of late hypoglycaemia. Patients do not seem to react with abnormal sensitivity, though this has been thought by some to be a theoretical objection to the use of insulin in anorexia nervosa.

At first a light diet is given. It includes fortified milk drinks and is steadily increased from 1500 calories to 4000 calories a day. In this way abdominal discomfort, which is often a frequent and frightening symptom in the early stages of treatment, is minimised. The patient's confidence is gained and reassurance is constantly given, but little attempt to uncover psychological problems is made until the patient's weight increases to near normal.

When treated with chlorpromazine and modified insulin patients gain weight rapidly, some cases increasing steadily by as much as 1 lb a day. The average time spent in hospital is shorter and the average weight gain is much greater with chlorpromazine than with other treatments (Table VIII).

However, a high proportion of these patients lose weight after leaving hospital, whether or not they continue to take chlorpromazine. Within two years of the time of discharge* about one-third of all first admission patients, however treated, will require readmission because of continuing weight loss[50]. The value of chlorpromazine in this and similar conditions therefore lies in its ability to rapidly restore lost weight. The problem of how to improve the long-term treatment of this often intractable condition remains. Drugs, given on an out-patient basis, are of little help, although antidepressant drugs are occasionally of value.

* These figures are based upon a personal long-term study of anorexia nervosa.

TABLE VIII

Hospital progress of anorexia nervosa patients

	Treatment with chlorpromazine and insulin	*Treatment with insulin alone*	*Bed rest without specific treatment*
	Group A $N = 30$	$N = 8$	*Group B* $N = 27$
*Average total weight gain	23 lb	18 lb	12 lb
Average time in hospital	36 days	59 days	44 days
*Average weight gain per week	4·7 lb	2·5 lb	2·2 lb
Average % pre-illness body weight regained	90%	84%	82%

* This difference is highly significant ($p < 0{\cdot}01$)

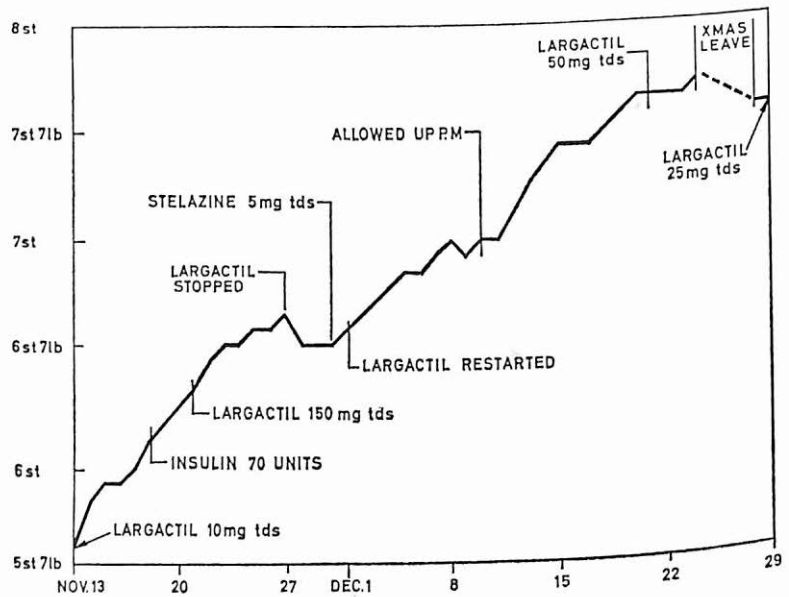


Chart of weight increase

PHENOTHIAZINES IN DISORDERS OF CHILDREN

Like other treatments given to psychotic children, phenothiazine derivatives give disappointing results and may even cause increased restlessness and tension. In fact virtually their only value is to control

disturbed behaviour in severely deteriorated children[2]. Hyperactivity, hostility, self-destructiveness, muteness and bizarre behaviour may be markedly reduced. Which phenothiazine is most effective in any one patient can only be determined by trial and error.

SIDE EFFECTS

These are directly related to dosage, although the amount of any phenothiazine compound necessary to produce side effects varies widely between patients. Disturbances of the cardiovascular and central nervous systems give most trouble.

Central nervous system. Extrapyramidal disturbances are most commonly caused by piperazine phenothiazines[78].

(1) *Parkinsonism.* Rigidity is sometimes marked and may be accompanied by a coarse tremor and excessive salivation. The term "chemical strait-jacket" is not inappropriate when these effects are severe.

(2) *Dyskinetic-dystonic reactions* are the result of sudden, usually shortlived, tonic contractions of localised groups of muscles. Numerous manifestations occur; torticollis, oculogyric spasms, opisthotonous, involuntary movements of jaw and mouth resulting in the mouth being either firmly closed or fixed wide open with tongue protruding, torsion spasms, and carpopedal spasms. Patients sometimes feel their tongue to be swollen[122] and have difficulty in speaking and swallowing.

These reactions usually occur at the start of treatment or if dosage is rapidly raised, and are transitory. Mild reactions will respond to reduction in dosage. More severe reactions, which are sometimes very frightening and painful to the patient, will respond quickly to intravenous promazine 25 mg or a barbiturate given intravenously. An antiParkinsonian drug should subsequently be given with the phenothiazine, but if dystonic symptoms recur the drug should be stopped or substituted by another phenothiazine. These reactions have been misdiagnosed as hysteria, tetany, and meningitis.

Acute dystonic reactions usually affect younger patients, men more often than women. Dyskinesia, which persists after discontinuing the phenothiazine, has been reported[61,174] after prolonged administration of the drug. AntiParkinsonian drugs are of no benefit in these cases but sedatives may help.

There is evidence that prolonged phenothiazine treatment of older patients, particularly those who have had a leucotomy operation or suffered brain damage, may result in the development of a syndrome of abnormal movements and dementia[94]. The abnormal movements are most marked in the face and tongue, and the syndrome closely resembles Huntington's chorea.

(3) *Akathisia* is an unpleasant form of restlessness, often localised

by the patient to his legs, which makes it difficult or impossible for him to sit still. The symptom is sometimes mistaken for agitation. Dosage should be reduced and an antiParkinsonian drug given concomitantly with the phenothiazine.

(4) *Muscular hypotonia* may occur, particularly with piperazine phenothiazines. Several patients taking trifluoperazine have reported sudden falls due to extreme muscle weakness, without loss of consciousness. This phenomenom seems to be potentiated by the presence of a MAO inhibitor.

(5) *Epileptic* attacks may occur. For instance a grand mal seizure occurred once in 17 per cent of anorexia nervosa patients within a fortnight of starting treatment with large doses of chlorpromazine[50]. Apart from temporary reduction of dosage no specific measures are required. Very rarely status epilepticus has been reported to occur and will then require the usual measures for this condition.

Cardiovascular system. Postural and orthostatic hypotension may occur and produce unpleasant effects: tiredness, weakness, dizziness, fainting. Hypertensive and senile patients are particularly liable to these effects, but they are by no means uncommon in other patients. The dosage required to bring about hypotensive symptoms is usually above 100 mg a day of chlorpromazine or its equivalent of another phenothiazine. Chlorpromazine and similar phenothiazines are more liable than piperazine phenothiazines to cause these effects.

If side effects are severe the phenothiazine dosage must be reduced. However, in a proportion of patients adaptation occurs after two or three weeks and symptoms lessen or cease.

As a result of lowered blood pressure, cerebrovascular and coronary thromboses occasionally occur in susceptible patients. More common is thrombosis in leg veins of bed patients receiving chlorpromazine, or following intravenous chlorpromazine.

Tachycardia occurs as a compensatory response to hypotension and as a result of the phenothiazine drug blocking vagal activity. Patients may complain of palpitations.

Very occasionally, during treatment with a piperazine phenothiazine blood pressure may be elevated.

Rarely, sudden death from ventricular fibrillation or cardiac arrest can occur in a patient treated with a large dose of a phenothiazine derivative[90].

Other common side effects include sleepiness, pallor, occasionally flushing of the face, headaches, a muzzy sensation, nausea, and constipation, less commonly diarrhoea. *Visual accommodation* is sometimes affected, causing blurring of vision. *Disturbances of micturition* include urgency, frequency and hesitancy in starting; incontinence is not uncommon in old people. Very rarely anuria occurs. Sexual functions are sometimes affected and ejaculation

inhibited. *Menstrual* disturbances, including amenorrhoea, swelling of breasts and even lactation[128] occur. *Weight* increase is sometimes marked[4], although this may be partly the result of water retention; phenothiazines, especially chlorpromazine, are liable to cause increased appetite and food intake.

False positive reactions to pregnancy tests may be given by patients taking phenothiazines[84].

Psychiatric side effects include confusional states and vivid visual hallucinations, usually with doses of 300 mg a day or more of chlorpromazine and generally in patients aged sixty and above; dosage should be reduced or else the drug should be substituted by another phenothiazine compound. Depression may occur in treated schizophrenics and patients with mania, especially with chlorpromazine, less often following the use of piperazine phenothiazines. Anxiety and depression sometimes develop in patients given chlorpromazine. These "paradoxical reactions" may disappear after one or two days, but sometimes call for the phenothiazine to be stopped or replaced.

TOXIC EFFECTS

An obstructive type of jaundice occurs in about 1 per cent or less of patients treated with chlorpromazine[11]. It is comparatively rare during treatment with piperazine phenothiazines. Pathologically there is biliary stasis due to swelling of the small biliary capillaries, and biliary thrombosis in the central canaliculi. Eosinophilia usually occurs concomitantly. Liver function tests vary, but the serum bilirubin and alkaline phosphatase are raised. Serum transaminase may also be raised.

This type of jaundice is considered to be an allergic response and is twice as common in women as in men. It usually occurs during the second or third week of treatment and is unusual after six weeks.

It is obviously advisable to stop the drug, although some authorities recommend continuing it in spite of jaundice, and it is probably wise subsequently to resume treatment with a different phenothiazine.

In the majority of cases, withdrawal of treatment is followed by full recovery, although jaundice may take as long as six months to disappear completely.

There is disagreement over the effects of prolonged chlorpromazine therapy upon the livers of patients. Some authorities claim that liver function tests and liver biopsies nearly always show some degree of liver damage[23]. There is evidence of melanin pigment deposition in many internal organs of patients receiving long-term chlorpromazine treatment, but the clinical significance of this is uncertain[73].

Pre-existent liver damage is not a contra-indication to treatment with chlorpromazine. There is no additional risk of jaundice in such

patients. Chlorpromazine should certainly not be withheld for this reason from an alcoholic patient admitted in delirium tremens.

Skin Reactions may develop during the first month of treatment, more commonly with chlorpromazine than with other phenothiazines.

Reactions take the form of erythema, macular or maculopapular rashes, and occasionally urticaria. Pruritus may be troublesome. With severe reactions it is best to stop the drug or substitute it by another phenothiazine, but in milder cases the drug can be continued along with symptomatic treatment such as an antihistamine preparation.

In about 10 per cent of patients receiving chlorpromazine, and a small proportion taking other phenothiazine derivatives, photosensitivity develops. Exposure to sunlight may then cause severe erythema and oedema of the exposed skin. Oedema of the knuckles and face, especially around the eyelids, may occur.

Photosensitivity, once developed, will not go until the causative drug is withdrawn, and will recur if the drug is restarted.

Contact dermatitis can be troublesome.

Pigmentation[37,99,111] following prolonged chlorpromazine treatment in high dosage has recently been described, and consists of a metallic bluish-brown discolouration of the skin of the face, neck, dorsum of the hands and legs, and other exposed areas. The pigmentation is due to an increase of melanin and the presence of a purplish coloured substance in the skin. Melanin may also be deposited in the eyes and internal organs. It seems that for pigmentation to occur the dosage of chlorpromazine must be of the order of 800 mg a day or more, in association with exposure to summer sunlight. On the theory that increased melanogenesis may reflect a basic defect in schizophrenia, Nicholson[136] has successfully treated schizophrenia by means of a low copper diet and a copper-chelating agent, D-penicillamine.

Retinal pigmentation, affecting vision, also occurs during treatment with thioridazine when the dosage exceeds 600 mg a day[125].

Blood dyscrasias

Agranulocytosis is a rare but occasionally fatal reaction to a phenothiazine[11], occurring between the sixth and tenth week of treatment. Fever, sore throat and oral infections should always call for a white cell count. Oral infection may be due to monilia which is encouraged by chlorpromazine[153]. If agranulocytosis is confirmed the phenothiazine should be immediately stopped and a broad spectrum antibiotic given. Leucopaenia is a fairly common transitory phenomenon in the first two months of treatment. It does not cause symptoms and does not require any action to be taken other than repeating the white cell count.

An *allergic purpura* has been reported during treatment with thioridazine and trifluoperazine.

Eosinophilia, up to 15 per cent, is not uncommon and is of no clinical significance. It frequently accompanies other toxic effects.

Miscellaneous effects include the enlargement of parotid glands[199] which may occur during treatment with thioridazine. Withdrawal of the drug results in the glands returning to their usual size.

OVERDOSAGE

Overdosage with chlorpromazine[58] and other phenothiazine derivatives results in profound depression of the central nervous system, sometimes preceded by epileptic fits. There is a considerable drop in blood pressure and the systolic pressure may fall to as low as 60 mm. Hypothermia develops and the body temperature may fall to a level at which cardiac arrhythmias occur. Paralytic ileus sometimes develops.

Treatment consists of gastric lavage, if the patient is seen in time, and nursing in a horizontal or head-down position. Intravenous fluids will be required and noradrenaline if hypotension is marked.

There is no specific antidote. It is best to allow recovery to proceed naturally under conservative symptomatic management. Unless body temperature approaches 85°F (29·5°C), when cardiac arrhythmias may develop, there is no advantage in actively trying to raise body temperature. Analeptics are of no value and should not be given.

COMBINATION OF PHENOTHIAZINES WITH OTHER DRUGS AND PHYSICAL TREATMENTS

Other treatments may be combined with a phenothiazine in order: (*a*) to bring under control more quickly a patient's disturbed behaviour; (*b*) to counteract side effects caused by a phenothiazine; or (*c*) to bring about a response in a patient refractory to treatment with a phenothiazine alone.

(*a*) PHENOTHIAZINES AND ECT

ECT alone is of little or no value in the treatment of schizophrenia (except in some cases of schizophreniform psychosis). But ECT is frequently given in conjunction with phenothiazine treatment, partly in order to control quickly difficult patients—an important practical detail when a patient with acute schizophrenia is treated in the ward of a general hospital—and partly because it is believed that the combination results in quicker, if not fuller, recovery. Of forty-six acute schizophrenic patients admitted during their first attack to the psychiatric unit of Westminster Hospital (a general hospital), forty, one received ECT in addition to phenothiazine drugs, half within

a week of admission. The average number of electroshocks given was nine (see Table VI, page 71). Similar reasons in the past led to ECT being given to many patients undergoing insulin coma therapy. It is unfortunate that no controlled trials comparing the results of treatment with phenothiazines alone and phenothiazines plus ECT have yet been done.

There are no contra-indications to giving ECT to patients receiving phenothiazine treatment. The early warnings of dangerous reactions[28,100a], particularly of cardiac arrest, appear to be without foundation.

(*b*) PHENOTHIAZINES AND ANTIPARKINSONIAN DRUGS

The large doses of phenothiazine drugs required to be given to control schizophrenia and other psychoses frequently cause extrapyramidal side effects. Although some authorities still maintain that there is a relationship between clinical improvement and the appearance of extrapyramidal symptoms, most people now believe that these side effects are undesirable and treat them with antiParkinsonian drugs. Indeed, it is routine practice in many units always to give an antiParkinsonian drug with large doses of a phenothiazine.

There are several antiParkinsonian drugs available:

benzhexol hydrochloride (Artane) 6–15 mg a day;
ethoproprazine hydrochloride (Lysivane) 150–300 mg a day;
benztropine methanesulphonate (Cogentin) 1–2 mg a day;
procyclidine hydrochloride (Kemadrin) 15–30 mg a day;
orphenadrine hydrochloride (Disipal) 150–300 mg a day.

From the point of view of controlling phenothiazine induced extrapyramidal side effects there is probably little to choose between them[164]. Orphenadrine is claimed to have an antidepressant action but it is doubtful in fact if this is more than occurs when any anti-Parkinsonian drug relieves extrapyramidal symptoms.

AntiParkinsonian drugs themselves may cause atropine-like side effects; dry mouth, headache, blurred vision, nausea, giddiness and tinnitus. Occasionally they may bring about a confusional state, hallucinations and agitation.

A man of 70 with paranoid delusions had, for several years, been well controlled by 15 mg trifluoperazine a day. Signs of Parkinsonism were then noticed and he was treated for this with orphenadrine 50 mg three times a day. After a week he returned complaining of visual and auditory hallucinations; he was aware of their hallucinatory nature but found them distracting and worrying. Orphenadrine was stopped and these symptoms ceased within twenty-four hours. They immediately recurred when orphenadrine was resumed a fortnight later. There were no side effects when orphenadrine was substituted for benzhexol.

Similar side effects have occurred in other patients treated with benzhexol, who were however able to tolerate orphenadrine.

(*c*) TWO PHENOTHIAZINE DERIVATIVES COMBINED

In general it is best to became familiar with two or three phenothiazine derivatives and use only these. Chlorpromazine is invaluable for controlling disturbed agitated psychotic patients. Trifluoperazine, thioproperazine, and fluphenazine are more useful in stimulating withdrawn apathetic schizophrenics. If one of these piperazine phenothiazines is given to a tense or agitated patient he is liable to become worse.

Particularly during in-patient treatment there may be reasons for combining two different phenothiazines.

An 18 year old female student was admitted with schizophrenia of about four months duration, after taking an overdose of butobarbitone. Outwardly she appeared to be emotionally "flat", withdrawn, and discussed her delusional ideas, albeit in woolly fashion, without any show of feeling. She was included in a trial of fluphenazine which was being undertaken at that time. She became increasingly tense and after five days made a second impulsive suicidal attempt. Fluphenazine was changed to chlorpromazine and ECT was given. She quickly settled down, became more relaxed and lost most of her delusional ideas. However she remained somewhat apathetic and showed little initiative during occupational therapy and discussion groups, The dosage of chlorpromazine was progressively reduced from 600 mg to 200 mg a day and trifluoperazine added, increasing from 5 mg to 15 mg a day. She began to show more emotion and initiative, to mix more easily and to pay more attention to her appearance. She was eventually discharged home on chlorpromazine 100 mg at night and trifluoperazine 10 mg twice a day.

A balance between schizophrenic apathy and tension is often easier to maintain, and allows for fine adjustments, when chlorpromazine is given at night and a piperazine phenothiazine during the day.

(*d*) PHENOTHIAZINES AND A BUTYROPHENONE COMPOUND

Haloperidol and trifluoperidol are sometimes effective in the treatment of chronic schizophrenic patients. If a patient fails to respond to treatment with a phenothiazine combining that drug with haloperidol or trifluoperidol may be helpful.

A man of 21, a clerk, was admitted with signs of schizophrenia: delusions, ideas of reference, thought disorder, depersonalisation, emotional incongruity and catatonic-like behaviour. He had been treated twelve months before with chlorpromazine and had remained inconstantly on a maintenance dose of that drug, unable to work. He was treated with chlorpromazine 600 mg a day and given 10 ECT (thrice weekly.) After three weeks there was no marked improvement.

Chlorpromazine was reduced to 300 mg a day and haloperidol 3 mg twice a day was added to his treatment. During the next fortnight his thinking became more rational, he became sociable, was cheerful and stable in mood, and showed more drive and initiative. He was discharged on 200 mg chlorpromazine and 3 mg haloperidol a day. He obtained work in a nursery garden, and was reasonably well adjusted when seen nine months later, still taking the same dosage of combined drugs.

(*e*) PHENOTHIAZINES AND ANTIDEPRESSANT DRUGS

Treatment of schizophrenia with a phenothiazine derivative may relieve psychotic symptoms but leave the patient depressed and lacking in drive and energy. Sometimes these depressive symptoms lift spontaneously, but often they persist. An antidepressant drug given together with the phenothiazine compound may then be helpful. This is particularly likely to be so in paranoid forms of schizophrenia where affect is often well preserved.

MAO inhibitors are, on the whole, best avoided in schizophrenia since, like amphetamine, they may exacerbate psychotic symptoms.

A man of 23 developed, nine months earlier, an acute schizophrenic illness which responded well to treatment with chlorpromazine and ECT. Subsequently he was maintained successfully on trifluoperazine 15 mg a day. Although his thinking and emotional responses appeared normal, his former drive and energy did not fully return, and he began increasingly to complain of this and of feelings of depression.

Phenelzine 45 mg a day was therefore added to the trifluoperazine. After a fortnight he felt more cheerful, and was able to concentrate better and to work more constructively. A month later he began showing signs of overactivity and shortly afterwards he was admitted to hospital in a state of catatonic excitement.

However, there are patients in whom MAO inhibitors produce a remarkable improvement.

A schizophrenic woman of 34, maintained on chlorpromazine 150 mg a day, felt a constant sense of depression. Amitriptyline was of no assistance. Isocarboxazid 10 mg twice a day was added to the chlorpromazine and depression lifted. She has remained on this drug, plus 150 mg chlorpromazine, for nearly two years with considerable benefit.

Amitriptyline is probably the safest antidepressant to prescribe to a schizophrenic patient, and is most effective when combined with a piperazine phenothiazine. The dose varies from patient to patient. Sometimes 50–75 mg amitriptyline at night is sufficient. In other cases dosage ranges from 50 mg to 150 mg a day and can only be determined by trial and error.

Some mixed manic depressive states can be stabilised by a combination of antidepressant and phenothiazine drugs.

Sometimes patients admitted with symptoms diagnostic of schizophrenia become increasingly depressed when treated with

chlorpromazine, and remain so as long as chlorpromazine is continued. It is important to recognise that some schizo-affective disorders may respond in this way to chlorpromazine. Alternatively, of course, a manic depressive illness may be misdiagnosed as schizophrenia. In these instances chlorpromazine should be substituted by another phenothiazine compound and an antidepressant drug given in addition.

(*f*) PHENOTHIAZINES AND INSULIN

(i) *Modified insulin* is used in cases of malnutrition and loss of weight. Although chlorpromazine alone often causes a rapid gain of weight, the addition of modified insulin may speed up this process.

The combination of chlorpromazine and modified insulin has its most spectacular success in the treatment of anorexia nervosa, which has already been described.

(ii) *Insulin coma therapy* is rarely used today. It is now doubted whether it has any *specific* effect on schizophrenia, although many patients undoubtedly benefited, mentally and physically. Much of the benefit probably derived from the attention given to patients receiving insulin coma, and to the group spirit that existed in an insulin coma unit.

Phenothiazine drugs appear to give better results in the treatment of schizophrenia, although some claims that insulin coma treatment results in fuller and longer lasting recovery are still made. If all else fails, insulin coma treatment is still worth considering.

An art student of 19 with a hebephrenic type of schizophrenic illness of about six months duration failed to improve with phenothiazines and ECT. Eventually he was given sixteen insulin comas, while continuing on chlorpromazine 300 mg daily. Improvement occurred in his thinking, emotional reactions and drive.

(*g*) PHENOTHIAZINES AND HYPNOTICS

Phenothiazines potentiate sedative and hypnotic drugs. This property is made use of in continuous narcosis, where large amounts of chlorpromazine are combined with quite small doses of barbiturates. In the past very large amounts of barbiturates were sometimes required for this treatment, which was not without danger. Considerably less barbiturate is required when chlorpromazine, up to 1000 mg a day, is also given.

Chlorpromazine 50–100 mg and a hypnotic drug are a powerful combination against insomnia. particularly when this is a symptom of depression.

RAUWOLFIA ALKALOIDS

Reserpine

Rauwolfia serpentina preparations have been used for centuries in tropical countries to treat madness and nervousness. In 1952 the alkaloid reserpine was isolated and shown to have the same hypotensive and sedating effects as the whole root.

Clinical investigations subsequently showed the drug to be of value in the treatment of schizophrenia. But at this time chlorpromazine was beginning to be introduced into psychiatry and reserpine, because of its unfortunate side effects, never became a popular treatment of schizophrenia.

In adequate dosage reserpine will reduce or abolish agitation and destructive behaviour, and cause delusions and hallucinations to fade or become less disturbing. Like chlorpromazine, reserpine controls schizophrenic symptoms but does not cure the illness.

Initially it was thought that reserpine was as effective as the phenothiazine derivatives. Clinical judgement now is that the phenothiazines are superior, more reliable in their effects, and less toxic and liable to cause troublesome side effects[22]. Phenothiazine derivatives have become the standard treatment for schizophrenia and reserpine is now only given to schizophrenic patients refractory to other treatments.

Reserpine is liable to bring out depression in predisposed individuals[133]. Severe depression develops in about 10 per cent of patients treated with reserpine, and it is inadvisable to give the drug to patients who have had past episodes of depression or who give a strong family history of depression. The drug is best avoided altogether in neurotic states. In fact, apart from schizophrenia refractory to phenothiazines and ECT reserpine has little use in psychiatry today. However, experimental work suggests that in combination with imipramine, reserpine may be useful in the treatment of some forms of endogenous depression.

ECT should not be given to a patient taking reserpine because of the danger of circulatory collapse and death. Since reserpine is a "hit and run" drug, its effects lasting long after treatment has stopped, it is as well to wait at least a week after stopping reserpine before giving ECT.

Reserpine can be combined with phenothiazine drugs, although there seems to be no advantage in such a combination. Hypotension is liable to be marked.

Reserpine should not be given to a patient taking a MAO inhibitor since the consequent release of free monoamines in the brain is liable to produce mania or a state of acute excitement.

DOSAGE

Reserpine may be given orally or by intramuscular injection. The dosage varies and is often limited by the development of side effects. As much as 60 mg a day has been given but the average dosage required in the treatment of schizophrenia is between 3–5 mg a day. Barse and Kline[14] described a somewhat complex scheme, giving 3 mg orally a day supplemented by intramuscular injections of up to 10 mg for several weeks.

SIDE EFFECTS

In the first few days of treatment, flushing, sweating, dryness of mouth, tremor, nasal stuffiness and drowsiness are liable to occur. After about seven days restlessness sometimes occurs, followed by pains in limbs, back and neck, signs of Parkinsonism, and increasing rigidity.

A curious combination of restlessness and drowsiness may appear. Frequency of and delay in initiating micturition, nocturnal enuresis, blurring of vision, cardiovascular and gastrointestinal symptoms, menstrual disturbances, lactation and oedema of face and ankles may occur. Appetite is sometimes considerably increased leading to overweight. One of the most serious complications of reserpine treatment is the development of severe depression.

BENZQUINAMIDE AND TETRABENAZINE (NITOMAN)

These are benzoquinolyzine derivatives, resembling reserpine in chemical structure and pharmacological and biochemical actions.

Both drugs have been used in the treatment of patients with chronic schizophrenia. If improvement is going to occur it will do so within two weeks of starting the drug, and the optimal effects are seen within about four weeks. They seem to be more reliable than reserpine, but not as effective as the phenothiazines in the treatment of schizophrenia. Side effects are similar to those of reserpine.

Dosage. This ranges from 75–100 mg a day of tetrabenazine and up to 800 mg a day of benzquinamide in the treatment of schizophrenia.

BUTYROPHENONE DERIVATIVES

The butyrophenones are another group of drugs effective in controlling psychotic behaviour and overactivity. The prototype, haloperidol (Serenace), was introduced into clinical psychiatry in 1959. Pharmacologically the butyrophenones are related to pethidine, although they have no narcotic nor analgesic effects.

Haloperidol

Haloperidol, and the more recent derivative triperidol, are useful in the treatment of mania, catatonic excitement and disturbed behaviour in psychotic or subnormal patients.

A woman of 34 was admitted to a psychiatric unit in a manic condition. She was given 200 mg chlorpromazine and 400 mg amylobarbitone sodium three times a day after admission, but her overactivity, talkativeness and tendency to interfere with the management of other patients was only partially lessened. Treatment was therefore changed. She was given 5 mg haloperidol intravenously and started on 3 mg orally twice a day. Within twelve hours there was a marked improvement and after three days she was virtually back to her normal self.

Agitation and restlessness in old people will sometimes respond particularly well to a small dose of haloperidol, 1·5–3·00 mg a day. In this type of case in particular, haloperidol is sometimes superior to chlorpromazine and other phenothiazine derivatives, not only in its therapeutic effects but also because it is less likely to cause hypotensive or hypothermic side effects.

An old lady of 82, living with her daughter, began without cause to worry about her finances, her family and so on. She was depressed. She would not agree to have ECT, although this had helped her to recover from past attacks. Chlorpromazine combined with imipramine lessened her agitation but made her feel tired, dizzy and unsteady on her feet. Chlorpromazine was replaced by haloperidol 1·5 mg twice a day. She relaxed, ceased to worry about trivialities and reverted to her premorbid personality.

Haloperidol is also sometimes helpful in the treatment of chronic schizophrenia unresponsive to other drugs and therapies. Some authorities[83,156] report that good results occur in cases of acute schizophrenia, but the evidence is not convincing that in such conditions the butyrophenones are as good as phenothiazines. However, individual cases may respond to haloperidol after weeks of unresponsiveness to phenothiazine derivatives and other treatments. The drug can be given alone but usually in the treatment of schizophrenia it is best combined with a phenothiazine.

A man of 22 had developed schizophrenia three years earlier. He had no hallucinations or other florid symptoms, but his thinking was woolly, his conversation off-centre and therefore difficult to follow, and his affect was impoverished and at times incongruous. He was considered to have simple schizophrenia. The treatment given was at first with trifluoperazine 30 mg a day, and six ECT were given. There was no response. Trifluoperazine was then replaced (over the course of a week) by haloperidol 12 mg a day. Extrapyramidal side effects developed and required treatment with oral orphenadrine, but a steady improvement occurred in the patient's symptoms. He was subsequently discharged home on haloperidol 3 mg twice a day.

DOSAGE

This ranges from 1·5 mg to 12 mg or more a day orally. To control hypomania, or to produce tranquillisation in a senile patient, 1·5 mg twice a day may be sufficient. When overactivity or aggressive behaviour are moderately severe a dosage of 3–6 mg twice a day will be needed. During the initial stages of treating schizophrenia 3–6 mg twice a day should be prescribed. Haloperidol is slowly excreted and a twice daily dose is sufficient to maintain a steady concentration of the drug.

In acute cases, when quick tranquillisation is required, the drug can be given intravenously or, if this is not possible, by intramuscular injection. Five mg haloperidol parenterally, repeated six hours later if necessary, will calm most patients.

The dosage of trifluoperidol is similar to that of haloperidol.

SIDE EFFECTS

Haloperidol is innocent of many of the side and toxic effects of the phenothiazines, although it has been suspected of causing jaundice[45]. Orthostatic hypotension and sensitivity reactions do not occur. But extrapyramidal symptoms are common, even using small doses, and include Parkinsonism, dystonic reactions and akathisia. Dystonic reactions are particularly liable to occur when haloperidol is administered intravenously.

Extrapyramidal effects can be lessened by starting with a small dose of haloperidol and increasing this slowly to the maximum therapeutic dosage. Acute dystonic reactions can usually be rapidly stopped by small doses of barbiturates, promazine or chlorpromazine, preferably given intravenously for quick effect. As with dystonic reactions following the use of a phenothiazine, they will often respond to authoritative suggestion.

There is no evidence that persistent extrapyramidal effects follow prolonged treatment with haloperidol, but it is sensible to use the drug in low dosage and for as short a time as possible in old people and brain-damaged patients.

Depression may follow treatment with haloperidol, particularly after recovery from manic states. Overactivity, elation and psychotic symptoms are replaced by a mood of despair. Similar depressive reactions occur during the course of treatment with phenothiazines. It is often difficult to know how much these are due to the drugs being taken and how much to the (treated) illness itself.

Combinations

(*a*) HALOPERIDOL AND ANTIPARKINSON DRUGS

Extrapyramidal side effects, particularly dystonic reactions, are relatively common during treatment with haloperidol. Although

some psychiatrists still maintain that a relationship exists between the appearance of extrapyramidal effects and clinical response, there is no convincing evidence of this to justify withholding antiParkinsonian drugs when using haloperidol in doses above 3 mg a day, or when extrapyramidal signs appear.

(*b*) HALOPERIDOL AND PHENOTHIAZINE DERIVATIVES

Although, statistically, the butyrophenones do not seem to be so effective as phenothiazines in the treatment of schizophrenia, there are individual patients whose symptoms respond more fully to haloperidol. There are also patients, usually with chronic anergic forms of schizophrenia, who respond best to a combination of haloperidol and chlorpromazine. Haloperidol stimulates and helps to break up psychotic behaviour patterns, while chlorpromazine prevents anxiety and tension from becoming too great.

A 26 year old man with a four-year history of schizophrenia was well behaved and his symptoms were controlled by chlorpromazine 400 mg a day. But he showed no initiative and was content to sit at home all day, doing nothing unless pushed into activity. He was given haloperidol 3 mg twice a day and chlorpromazine was reduced to 100 mg at night. He became tense and restless at first, but when chlorpromazine was increased to 50 mg three times a day and 50 mg at night, tension subsided. He showed more drive and better affect and was at last persuaded to attend a rehabilitation course.

A combination of haloperidol and chlorpromazine given parenterally is useful in rapidly controlling acute mania or catatonic excitement.

A young well-built woman, under treatment for the past three years for violent manic depressive swings of mood, suddenly developed acute mania while at home. She became virtually unmanageable for a time but eventually allowed herself to be given intramuscularly 10 mg haloperidol and 100 mg of chlorpromazine. This had remarkably little effect upon her activity and alertness, but did, after about an hour, make her less aggressive and more prepared to accept further treatment. She was now given a further 5 mg haloperidol, 150 mg chlorpromazine, and 400 mg amylobarbitone sodium intravenously. She became drowsy and allowed herself to be taken to a psychiatric unit for treatment.

(*c*) HALOPERIDOL AND ANTIDEPRESSANT DRUGS

Mixed manic depressive states and patients who have rapid and frequent swings of mood are difficult to control, but a combination of haloperidol with an antidepressant drug is sometimes effective. Of the tricyclic antidepressants at present available it is probably best to use amitriptyline for this purpose. Isocarboxazid is the safest MAO inhibitor, although iproniazid is sometimes more effective. Which antidepressant to give in any one case will depend upon

the clinical picture, but more often than not is a matter of trial and error.

A woman of 46, who had experienced her first attack of depression in her mid-twenties, had become almost totally disabled by mixed manic depressive symptoms. She alternated throughout the day between elation and tearful self-recrimination, was hypersensitive, took offence easily and was an impossible companion. She had had numerous and varied treatments in the past and modified leucotomy was now being considered. She was given haloperidol 1·5 mg twice a day and iproniazid 25 mg three times a day. Within a week there was an improvement in her symptoms and this continued for the next two months. Her mood became more cheerful and consistent, she was easier to live with and no longer quarrelled all the time with her husband.

She has remained on this combination for the past three years. From time to time the dosage of either drug has been varied, depending on her clinical state, but it is apparent that symptoms, although generally well controlled, are still present beneath the surface.

A pyknic man of 48 had developed manic depression ten years earlier. Depression and mania alternated, without any intervening period of normality, each phase lasting about three months. Treatment including ECT had not been of much assistance. A combination of haloperidol 1·5 mg twice a day and amitriptyline 50 mg three times a day was given. Side effects were troublesome at first until orphenadrine 50 mg three times a day was added and amitriptyline was reduced to 100 mg a day. He has been reasonably stable for the past year although he is still aware of mild mood changes every three months. When cheerful he reduces amitriptyline to 50 mg a day. When depression recurs he increases this dose to 150 mg a day for a fortnight and then to 100 mg a day. The dosage of haloperidol varies between 0·75 mg–3 mg a day.

(*d*) NEUROLEPTANALGESIA[138]

This is a procedure in which a neuroleptic and an analgesic drug are combined to produce varying degrees of "wakeful anaesthesia", the patient being tranquil, analgesic and co-operative. This procedure is, of course, an extension of Labourit's use of chlorpromazine, promethazine and other drugs in his "cocktail lytique". Phenothiazines and butyrophenones have each been used as the neuroleptic, but the butyrophenones, especially Droperidol, have the advantage of inducing more intense catalepsy with a greater margin of safety. The usual dosage is Droperidol, 10 mg, or haloperidol 5 mg, given about one hour before operation.

(*e*) HALOPERIDOL AND ECT

There is no contra-indication to this combination.

Trifluperidol

This is a butyrophenone derivative with a piperazine ring attached to the third carbon atom of the straight propylene chain.

This drug is similar to haloperidol in its effects, although it is more powerful weight for weight. It is said to relate to haloperidol as trifluoperazine does to chlorpromazine. Claims have been made for its efficacy in schizophrenia but there is no convincing evidence that any of the butyrophenone derivatives is as effective as the phenothiazine derivatives, which should remain first choice of treatment.

Dosage varies from 1 mg to 10 mg a day given in two divided doses.

LITHIUM SALTS

Lithium salts were used for the treatment of gout and rheumatic disorders over one hundred years ago. It was not until 1949 that Cade[36] described their value in the treatment of states of psychotic excitement and lithium salts began to be used in manic depressive conditions. That the value of lithium in manic states has not become more widely recognised is probably due to the advent of the phenothiazine derivatives and other major tranquillisers, to the comparatively small numbers of patients requiring treatment, and to the reputed toxicity of the lithium ion.

Lithium carbonate is the least toxic salt and the one most used. Like other drugs used in the treatment of mania, symptoms are controlled, not cured, and lithium carbonate has to be continued until the illness remits spontaneously.

CLINICAL USES

Lithium carbonate is an effective treatment of mania and hypomania[82,161]. Alone or in combination with an antidepressant drug it can sometimes stabilise and prevent further manic depressive swings of mood.

B., a man of 39, had experienced bouts of alternating hypomania and depression since his late twenties. In the past hypomanic episodes had been treated with chlorpromazine and various sedatives, with only limited success. He was seen at the start of his seventh attack of hypomania. He was overactive, talkative, full of new ideas relating to his work (some of which he had already put into effect), irritable, insensitive, and was sleeping and eating little. He was given 2 g lithium carbonate a day, and after five days showed considerable improvement. Lithium was then gradually reduced to 750 mg a day. Depressive symptoms followed about a month later, but responded to amitriptyline 50 mg three times a day added to the lithium. He remained on a combination of lithium carbonate 250 mg and amitriptyline 25 mg both three times a day and

had no attack of hypomania or depression for eighteen months. He then went on holiday and stopped all drugs. Within a month of his return home hypomanic symptoms began to reappear. These again responded fully to the same drug combination.

It seems that lithium may relieve depressive as well as manic symptoms, although this needs confirmation. Certainly the combination of lithium and amitriptyline can be an effective mood stabiliser.

Although lithium is best in acute mania, chronic manic states may also respond to treatment with the drug.

A woman of 36 had been hypomanic for four years. She was overactive, although achieving little, and talked incessantly. She had lost most of her friends because of her tactless behaviour as well as her job as a teacher. She had become a heavy drinker and promiscuous in her habits. She responded to treatment with lithium carbonate and, on a maintenance dose of 0·75 g a day, was able to return to teaching.

A disadvantage of lithium carbonate, compared to other drugs useful in the treatment of mania such as chlorpromazine and haloperidol, is the comparatively long time that may lapse after starting treatment before its effects appear. If a patient is acutely manic, it is sometimes advantageous to combine lithium carbonate with chlorpromazine for a week or so, until the patient is co-operative.

G. was admitted in acute mania. He was aggressive and at times unco-operative, although he could be persuaded with difficulty to take his medication. Lithium carbonate 2 g a day was given for five days, and then progressively reduced to 1 g a day. Chlorpromazine was also given for the first ten days, starting with 600 mg a day and steadily reducing this dosage after five days. He was then maintained on a dosage of lithium carbonate alone varying between 750–1500 mg a day.

Atypical manic depressive illnesses, or schizo-affective illnesses, may also respond to treatment with lithium carbonate.

A woman of 27 was seen during the course of a third schizo-affective illness. She was elated, talked continuously about her visions and about how she had heard God speaking to her, laughed and cried alternately and refused to eat, drink or sleep. She was initially given haloperidol 5 mg intravenously, and then 1·5 mg twice a day orally for a week, together with lithium carbonate 2 g a day. She rapidly lost her symptoms. Within a fortnight she was able to return home on a maintenance dose of 750 mg a day of lithium carbonate.

Recurrent illnesses of this nature which respond to lithium carbonate are probably of an affective nature, as Fish has suggested. Schizophrenic illnesses are not usually helped by lithium carbonate unless there is a strong affective component also present.

Trials carried out with lithium have been mostly of the uncontrolled type and are unreliable because of the tendency for mania to vary or remit spontaneously. None the less, the results of trials such

as those of Schou and others[82,175], where manic patients were treated alternatively with lithium and a placebo, and double blind studies such as that of Maggs[123], all confirm that lithium is effective in a high proportion of manic states.

DOSAGE

The starting dose of lithium carbonate in the treatment of mania is between 2–3 g a day, given in three divided doses. This dosage should be progressively reduced after a week to a maintenance dose of 0·5–0·75 g a day. Some authorities believe that it is advisable to withhold the drug one day a week in order to prevent accumulation of lithium and minimise possible side effects. When mania is severe, other drugs such as chlorpromazine, or ECT, can be given concomitantly with lithium.

SIDE EFFECTS

Lithium is thought to bring about its effects by replacing sodium in the body, particularly in the central nervous system. However, the exact mode and mechanism of this action is far from clear[44]. The lithium ion's behaviour resembles sodium in some tissues and enzyme systems, but is more like potassium in others. There is probably always some risk to the patient with lithium, particularly when daily dosage exceeds 750 mg. It is important therefore to maintain careful clinical control in order to minimise risk of intoxication. Biochemical control is also helpful but is not always available. Toxic symptoms are liable to appear when serum lithium exceeds 2·0 ml Eq/L.

Patients when manic seem to be less likely to develop toxic symptoms than non-manic patients. The tolerance of manic patients for lithium often decreases when mania subsides, which suggests the possibility of this being related to the sodium changes known to occur in manic depressive disorders.

Any system of the body may be affected but the ones most commonly involved are the gastrointestinal and central nervous systems.

Anorexia, nausea and diarrhoea are early symptoms, and these indicate that the dosage of lithium should be reduced. Less frequent but equally significant are tinnitus, giddiness and ataxia, drowsiness, difficulty in focusing, fine tremor, thirst and polyuria. If the serum level of lithium continues to rise diarrhoea and vomiting are liable to increase, the patient may become confused, develop epileptic fits, and pass into coma.

Changes in the electrocardiograph (ECG) are common, even in the absence of toxic symptoms. These include flattening or inversion of the T wave[189]. Electroencephalograph (EEG) changes also occur. Both ECG and EEG changes are reversible when lithium is stopped.

One considerable advantage of lithium carbonate over phenothiazines in the treatment of mania, particularly in long-term maintenance therapy, is the absence of drowsiness and tiredness. In fact, provided lithium does not accumulate and reach toxic levels, it causes virtually no side effects.

INTOXICATION

Lithium should be stopped at once if signs of toxicity develop, and resumed on a lower dosage when all toxic symptoms have disappeared after a few days. In serious cases of lithium poisoning, continuous gastric suction and replacement of fluids and electrolytes lost may also be required. Biochemical control is advisable.

CONTRA-INDICATIONS

Patients with heart failure, renal failure, Addison's disease, or any condition liable to upset the balance of sodium should not be given lithium salts.

COMBINATIONS

Lithium carbonate may be safely combined with any other drug, or with ECT.

CHOICE OF DRUG FOR TREATMENT OF MANIA

Lithium, chlorpromazine and other phenothiazine derivatives, or haloperidol

It is impossible to lay down hard and fast rules, for no good comparative trials have been reported and much will depend on the individual experience of the therapist.

In large doses, over 2·0 g a day for more than a fortnight, lithium carbonate probably carries more risk of serious side effects than chlorpromazine and haloperidol unless biochemical control can supplement clinical observation. However, as described above, severe states of mania are best treated initially with a combination of lithium and chlorpromazine or haloperidol. Subsequently, when acute symptoms are controlled, lithium alone can be continued.

Lithium carbonate rarely causes side effects in a maintenance dose of 0·5–0·75 g a day, and many patients prefer it to chlorpromazine or haloperidol for this reason.

But the therapist must be prepared to use any of these drugs, alone or in combination, on individual cases of mania which are not responding to treatment.

OXYPERTINE

This is a tryptamine derivative, an indolylalkylphenylpiperazine, which is claimed to be effective in the treatment of schizophrenic illness, particularly in chronic cases. In spite of some favourable reports, it is doubtful whether the drug is superior to phenothiazine derivatives. In dosages of up to 120 mg a day oxypertine will stimulate some apathetic withdrawn schizophrenic patients, and result in improved behaviour and increased communication[58]. More careful studies are required before it can be accepted that this drug is effective and in what type of psychotic illness. Side effects include extrapyramidal symptoms, increased anxiety, and giddiness.

THIOXANTHENE DERIVATIVES

These drugs are closely related to the phenothiazines. Chlorprothixene (Taractan) has been used in the treatment of affective and schizophrenic illnesses. It has quite a marked sedating effect in dosage of up to 300 mg or more a day, but it is not comparable in effectiveness to phenothiazine derivatives in the treatment of schizophrenia, nor to antidepressant drugs in depressive illness.

CHAPTER IV

DEPRESSANT DRUGS—II

MINOR TRANQUILLISERS, SEDATIVES AND HYPNOTICS

Numerous drugs are used in the treatment of anxiety. But anxiety is a ubiquitous symptom and it is important to know what is meant by the word.

Anxiety may be a normal reaction of someone to unpleasant circumstances. On the other hand, the anxiety felt or shown by an individual may appear to be without foundation or out of all proportion to the supposed cause. Anxiety can occur as a symptom in almost any psychiatric syndrome or organic disease. It is essential, for treatment purposes, to distinguish a primary anxiety state from anxiety which is secondary to, and may mask, depression, schizophrenia, organic disease or an early state of dementia.

It is sometimes very difficult, if not impossible, to distinguish clearly on clinical grounds alone, between an anxiety state and reactive depression. Depression may be *assumed* retrospectively because symptoms respond to antidepressive treatment and not to tranquillisers or sedatives alone.

On the other hand secondary symptoms, such as depression, hysteria, or obsessional thinking, tend to complicate the picture if anxiety has lasted for any length of time, so that *pure* anxiety states are not commonly seen in clinical practice. It may be that there is no basic distinction between an anxiety state and reactive depression, only a difference in underlying personality structure and a greater or lesser degree of reactivity.

Knowledge of the basic personality of the patient presenting with anxiety is always helpful in diagnosis. The inadequate personality who reacts to relatively minor stress with excessive anxiety is less likely to have a depressive condition underlying his anxiety symptoms than the anxious patient who has always, until now, dealt adequately with his responsibilities and difficulties. In general, therefore, inadequate personalities with anxiety symptoms will respond to tranquillisers and sedatives alone. More adequate personalities, particularly when anxiety symptoms occur for the first time after the mid-twenties, usually respond better to the combination of a MAO inhibitor and a tranquilliser. (See Table IX.)

The barbiturates are still, in many cases, unsurpassed in their ability to relieve anxiety. But they are liable to cause addiction in predisposed personalities, and a suicidal attempt is more likely to be successful with them than with the minor tranquillisers. Some patients do undoubtedly respond better to chlordiazepoxide or meprobamate than to a barbiturate, although it is difficult to isolate clinically any particular characteristic of such patients which might enable them to be distinguished when first seen.

TABLE IX

Response (partial) to drugs other than MAOI

Drug	*Group 1**	*Group 2**	*Group 3**
Barbiturates (medium acting)	0	21%	91%
Chlordiazepoxide	0	61%	64%
"Drinamyl"	85%	86%	82%

* Three groups of patients with similar symptoms of anxiety and depression were differentiated on the basis of their response to drugs. Group 1 responded to a MAO inhibitor alone. Group 2 responded best to a combination of a MAO inhibitor and chlordiazepoxide. Group 3 failed to respond or were made worse by a MAO inhibitor. The three groups were similar in respect of age and sex. Patients of groups 1 and 2 were all of adequate personality. Group 3 patients were inadequate personalities[168].

A tranquilliser or sedative may be useful even when there is a reasonable cause for extreme anxiety. The patient may be physically and mentally affected by his anxiety to such a degree that, although previously able to deal with the situation, he now collapses and cannot deal with his difficulties. This engenders even more anxiety and a vicious circle is set up. Treatment should aim to break this vicious circle: to reduce anxiety to a level at which the patient can function efficiently and deal with his problems. Once this is done treatment can usually be tailed off and stopped. Sometimes it is only necessary to treat the insomnia which may result from anxiety. Some patients seem to displace all their anxiety onto difficulty in getting to sleep or tendency to waken frequently and work themselves into a state of panic as bedtime approaches. An effective hypnotic which ensures a good night's rest will break this vicious circle and lead to all round lessening of anxiety. Since anxiety is all too easily displaced, and is liable to cause secondary symptoms, the sooner it is effectively treated the easier treatment is likely to be.

BARBITURATES

Barbiturates have been used clinically for over fifty years as sedatives and hypnotics. Numerous tranquillisers have come and gone over the past ten years but the barbiturates have retained their popularity among practitioners as effective and rapid alleviators of anxiety. They are safe from side effects, are reliable, and are a useful yardstick to measure the action of new sedatives and tranquillisers.

Barbitone (Veronal) was introduced into clinical practice in 1903, phenobarbitone in 1927.

It is still customary, although questionable, to divide barbiturates into three groups, depending on their action: long, medium, and short acting. Long acting barbiturates (more than eight hours) such as phenobarbitone, are useful sedatives but poor hypnotics. Short acting barbiturates like thiopentone are valuable in producing anaesthesia, but have no role as sedatives. It is the medium acting barbiturates like quinalbarbitone, butobarbitone, pentobarbitone and amylobarbitone sodium which are most used in psychiatric practice, both as hypnotics and as sedatives. In addition, intravenous amylobarbitone sodium is invaluable in dealing with acute panic reactions and states of psychiatric shock, and, in conjunction with parenteral chlorpromazine, in controlling acutely disturbed patients.

As with other drugs patients vary widely in the way they react to barbiturates and in the rate at which they absorb, metabolise and break the drugs down. Thus, while it is true for most people that phenobarbitone is a poor hypnotic, there are patients who sleep soundly and wake without a hangover on a dose of 200 mg; and, there are patients who wake up rather than become sleepy on 200 mg of amylobarbitone sodium.

There is no good evidence that any of the medium acting barbiturates is a better hypnotic or sedative than another. Which one is used will depend on the doctor's preference and upon the patient. Pentobarbitone may leave a patient with a hangover for most of the morning after wakening while butobarbitone may not. With another patient it may prove to be the converse.

Correct dosage is important, but again individual variation is wide. A small dose of say quinalbarbitone (45 mg) which calms one patient may either have no effect or produce too much sedation in another. Similar variation occurs when a hypnotic dose is given.

Barbiturates have no analgesic action. On the contrary there is evidence to suggest that their use may decrease a patient's tolerance to pain. When prescribing either a sedative or hypnotic dose of a

barbiturate for a patient who is in pain, an analgesic should therefore always be given in conjunction with the barbiturate.

Children can tolerate large doses of barbiturates (relative to adults), often without noticeable effect. Barbiturates are sometimes useful in calming children and sending them to sleep, but not when they are severely disturbed. Paradoxically amphetamines are then sometimes more effective, but a phenothiazine or minor tranquilliser such as chlordiazepoxide is usually a better choice of drug.

Prolonged treatment with barbiturates will sometimes itself create a chronic tension state. Increasing doses may be required, which when not met results in a continuous mild state of withdrawal tension. It is important to know that the good effects of MAO inhibitors are often blocked if the patient is receiving too large a dosage of barbiturates; these drugs must be reduced or stopped and substituted by a minor tranquilliser.

SIDE AND TOXIC EFFECTS

Barbiturates are relatively free of serious side effects. Some patients complain of sleepiness or excessive sedation, in which case the dosage should be reduced or a change made to another barbiturate or to a tranquilliser. With elderly patients barbiturates should, as a general rule, be avoided since they are liable to bring about or increase a confusional state. It is better when prescribing a hypnotic for an elderly patient, to give a nonbarbiturate such as gluthethimide, if necessary potentiated by chlorpromazine.

Addiction and habituation may occur in predisposed personalities and lead to a state of barbiturate confusion and intoxication; vertigo, ataxia, nystagmus, visual hallucinations, muscle weakness and hysterical or childlike behaviour. When large amounts of barbiturates have been taken the drug must never be suddenly stopped because epileptic fits, sometimes progressing to status epilepticus, may then occur. Withdrawal symptoms develop within twenty-four hours of stopping the drug, and reach a peak over 2–3 days. In addition to anxiety, insomnia, tremor, dizziness, nausea and vomiting, the addicted individual may develop a state resembling alcoholic delirium tremens or, occasionally, a psychotic episode. Barbiturates should be slowly but progressively withdrawn over the course of about a week, covered if necessary by chlorpromazine. Rees[160] states that at least 0·5 g (8 gr) of barbiturate three times a day for 4–6 months must be ingested before *physical* dependence occurs.

Reaction times of anyone taking a barbiturate are invariably prolonged to some extent, a fact which all drivers should know. Alcohol, and other drugs such as antidepressants and phenothiazines, will increase this and other side effects.

Toxic or sensitivity reactions are rare. Skin reactions, and very rarely agranulocytosis, occur mainly with phenobarbitone.

CONTRA-INDICATIONS

These are a history of intermittent porphyrinuria, myxoedema, myasthenis gravis or a previous sensitivity reaction to a barbiturate compound.

Although barbiturates are metabolised in the liver there is no convincing evidence that patients with cirrhosis of the liver, unless liver failure is impending, are more susceptible to the effect of barbiturates than patients without cirrhosis. However, as in patients with renal disease, there may be some interference with the breakdown of barbiturates and a prolonged reaction in consequence.

OVERDOSAGE

Between 1951 and 1959 the amount of barbiturates prescribed almost doubled, and there has been a steady increase in the number of deaths from barbiturate poisoning[137]. In 1961 there were more than 1000 such deaths in England and Wales.

Deaths may occur as a result of suicide or accident. A not uncommon happening is for a patient to wake up at night in a partially confused state after taking a hypnotic dose and, not remembering, take more of the drug. As a result he may inadvertently kill himself. The chances of this happening are increased if the patient has drunk alcohol before going to bed.

Barbiturate poisoning still has a mortality of between 2 and 5 per cent[31], due to respiratory and cardiovascular depression and to the consequences of prolonged unconsciousness. Treatment involves gastric lavage, if the patient is seen within two or three hours of taking the drug, maintaining blood pressure with noradrenaline if necessary, and intubation or tracheotomy if need be to maintain a satisfactory airway. Where facilities exist dialysis will sometimes make the difference between life and death, especially when long acting barbiturates have been ingested. The anti-diuretic effects of barbiturate poisoning may be combated by giving an infusion of manitol. An antibiotic will help to prevent secondary infection if coma is prolonged[42].

Giving analeptics such as picrotoxin or bemegride does not hasten recovery and is inadvisable. A combination of bemegride and amylobarbitone sodium (Mylomide) is marketed, on the assumption that this mixture is safer to give a potentially suicidal patient than the barbiturate alone. The evidence on which this is based is shaky[142]. For similar reasons, barbiturates are also combined with ipecacuanha alkaloids in the hope that an overdose will cause emesis. But not all patients will vomit.

(*a*) LONG ACTING BARBITURATES

(i) *Phenobarbitone*

Phenobarbitone is useful in the treatment of chronic anxiety states, particularly in those patients who have always reacted to minor stresses with excessive anxiety. It is not uncommon to meet patients who have been on a small daily dose for years and who are obviously habituated to the drug. There seems little point in trying to wean them off phenobarbitone and upsetting their somewhat precarious equilibrium, unless the drug is depressing them.

Acute anxiety does not respond so well to phenobarbitone and is better treated with a medium acting barbiturate, such as amylobarbitone or quinalbarbitone.

Phenobarbitone as a rule is useless as a hypnotic although there are patients who take it at night and have even become habituated to a nightly dose. For instance, a man of sixty with a chronic anxiety state has been taking 1·2 g (20 gr) of phenobarbitone a night for over twenty years without apparent ill effect. An attempt to reduce the dose resulted in such a disturbance that it was deemed wise to leave well alone.

Phenobarbitone should be used cautiously in older patients and avoided altogether if there are signs of depression. The drug is liable to bring out or increase depression, and may precipitate a suicidal attempt.

> An accountant of 42 had been diagnosed by his general practitioner as having an anxiety state, and treated with 30 mg phenobarbitone three times a day. In fact his symptoms were those of an agitated depression. Depression deepened rapidly after he started to take phenobarbitone and three weeks later he attempted suicide by swallowing all his tablets.

It is still not widely enough recognised that anxiety states occurring for the first time in middle age or later are nearly always secondary to depressive illnesses.

Phenobarbitone is useful in children as a temporary means of reducing excessive excitement and hyperactivity, and encouraging sleep. Unlike adults, young children and infants may sleep soundly on a small dose of phenobarbitone. Treatment will sometimes break a vicious circle by allowing a difficult child's mother to have a sound night's sleep and so decreasing her tiredness and tension.

Phenobarbitone is mainly broken down slowly in the liver, but about 20 per cent is excreted unchanged by the kidneys. Its duration of action is more than eight hours.

(ii) *Intramuscular phenobarbitone*

Up to 200 mg is useful if the drug cannot be given by mouth. For instance, 200 mg of phenobarbitone given intramuscularly immediately after ECT will usually ensure that a patient continues to sleep for several hours after his treatment and awakens in a calm state. This is particularly helpful when patients are very tense.

The use of phenobarbitone as an anticonvulsant is not discussed here.

(*b*) MEDIUM ACTING BARBITURATES

Amylobarbitone sodium

Unlike most barbiturates, amylobarbitone sodium is soluble and can be given intravenously if necessary.

Intravenous amylobarbitone sodium 400–600 mg in 10 c.c. of water, given over the course of a minute or longer, is a most effective way of dealing with overwhelming anxiety and panic, of quickly inducing relaxation and sleep, and so avoiding the secondary complications which may arise if severe anxiety is allowed to persist.

Amylobarbitone sodium, together with chlorpromazine or haloperidol, may be invaluable in controlling a manic or catatonic patient. A schizophrenic man was threatening to kill his wife and had already wounded her and set fire to part of their house. He was at length persuaded to agree to intravenous injection of amylobarbitone sodium 600 mg and chlorpromazine 100 mg. Within a few minutes he was asleep and on his way to hospital.

If the intravenous route is impracticable, 400 to 600 mg of amylobarbitone sodium by mouth, depending on the patient's age and weight, together with 100 mg chlorpromazine, will usually produce a deep and prolonged sleep within 20–30 minutes. Subsequent sedation will usually be at a reduced dosage, unless continuous narcosis is the aim.

During continuous or semi-continuous narcosis, 200–400 mg of amylobarbitone sodium three or four times a day, together with chlorpromazine, may be required when treatment is first begun. Later, when the patient's resistance has been overcome and he is sleeping soundly for much of the day, the dosage can be reduced to the minimum needed to maintain a satisfactory depth of sleep.

60–120 mg amylobarbitone sodium is an effective sedative to give an anxious or phobic patient. Unlike phenobarbitone, but like alcohol, small doses of medium acting barbiturates often produce a mild sense of euphoria as they relieve tension. Some patients with chronic tension states may need to continue to take a sedative dose of amylobarbitone sodium for years, intermittently or continuously. Inevitably, therefore, there is a risk of habituation or addiction in

some predisposed personalities. It is as well to avoid barbiturates when treating patients of this type. For example alcoholic patients, who are frequently tense, anxious people, may be weaned off alcohol only to become addicted to barbiturates.

A man of 32 had been drinking a bottle of whisky or more a day for the past seven years. He was "dried out", using chlorpromazine and amylobarbitone sodium, and put on to disulphiram. Subsequently he was followed up and treated with supportive psychotherapy and amylobarbitone sodium 60 mg three times a day. Within four months he was on a daily dose of 750 mg and required re-admission to hospital.

60 mg of amylobarbitone sodium will often allow a phobic patient to deal with the situation he fears and is unable to face; to travel by air or by public transport, to go into a crowded or unfamiliar shop, to eat at a restaurant or, in the case of a housebound housewife, just to go out of doors. Even the good personality patient whose phobic anxiety symptoms often respond best to the combination of a MAO inhibitor and a tranquilliser may be helped in the early stages of his treatment by amylobarbitone sodium. Sometimes the mere knowledge that he has a few tablets of the barbiturate in his pocket is enough in itself to prevent anxiety developing and to give the patient confidence to overcome his fears.

Amylobarbitone sodium, or any other medium acting barbiturate, is an effective hypnotic. Which drug is used and the dosage given must depend on the reason for the patient having insomnia. It is useless giving a barbiturate to a patient in pain unless an analgesic is also added. An anxious patient unable to get to sleep, say on his first night in hospital, may only need a small dose of amylobarbitone sodium (60 mg) to reduce his anxiety in order to sleep profoundly. Another anxious patient may waken frequently through the night unless given 200 mg amylobarbitone sodium.

A patient with an agitated depressive state may get off to sleep on 200 mg amylobarbitone sodium but will waken again after a few hours, sweating and worrying. He may require 400 mg with 100 mg chlorpromazine. This combination will usually give a good eight hours sleep. Large doses of barbiturates are best avoided in elderly patients and in patients who easily become confused. It is then better to give chlorpromazine with a non-barbiturate hypnotic.

(*c*) SHORT ACTING BARBITURATES

Thiopentone (*Pentothal*)

Thiopentone, because it is poorly absorbed orally, is given intravenously and rapidly produces anaesthesia. 250 mg in 10 c.c. water

is usually sufficient for psychiatric purposes. The drug has been, and still is, used to bring about an "abreaction" and to terminate hysterical conditions, although amylobarbitone sodium is usually preferred because it is safer.

In 1959 Roth[163] described the *calamity syndrome*, a phobic anxiety-depersonalisation state with symptoms resembling temporal lobe function disturbance, occurring predominantly among women, which followed a disastrous or painful event. Claims were made for the successful treatment of the syndrome by means of intravenous thiopentone given on alternate days to produce light sleep.

When symptoms have existed for a short time only such treatment does seem to meet with a high rate of success (as do other forms of therapy). When symptoms have persisted for longer, and where the previous personality was reasonably adequate, a MAO inhibitor combined with a tranquilliser such as chlordiazepoxide is often effective when thiopentone treatment fails.

Thiopentone should not be given to a patient with a full stomach, for fear that food may subsequently be regurgitated and aspirated into the lungs during unconsciousness. Laryngeal spasm may be caused by thiopentone, and the drug should not therefore be given unless oxygen and apparatus for establishing a clear airway are available.

TREATMENT OF BARBITURATE ADDICTION

Treatment of barbiturate addiction is similar in essence to the treatment of any other form of addiction. The drug must be completely withdrawn, but slowly in order to avoid the occurrence of epileptic fits and other withdrawal effects. Psychotherapeutic support will be needed and it is best to avoid giving any drug. If this is not possible, a tranquilliser such as chlordiazepoxide 5–10 mg three times a day is to be preferred to meprobamate because it is less addictive.

COMPARISON OF BARBITURATES

Qualitatively, all the barbiturates have the same action, and they differ only in the rate and method of disposal in the body.

As stated above, the medium acting barbiturates do not differ one from another as hypnotics or sedatives to any appreciable extent.

TABLE X

Dosage of Barbiturates

	Single Sedative dose	*Hypnotic dose*
Long Acting		
Barbitone sodium (Medinal)	—	320–500 mg (5–10 gr)
Phenobarbitone	15–60 mg (¼–1 gr)	—
Medium Acting		
Amylobarbitone	30–100 mg (½–1½ gr)	200–400 mg (3–6 gr)
Amylobarbitone sodium	60 mg (1 gr)	200–400 mg (3–6 gr)
Butobarbitone (Soneryl)	—	100–200 mg (1½–3 gr)
Nealbarbitone (Censedal)	60–200 mg	—
Pentobarbitone sodium (Nembutal)	—	100–200 mg (1½–3 gr)
Quinalbarbitone sodium (Seconal)	45–100 mg (¾–1½ gr)	100–200 mg (1½–3 gr)
*Tuinal	—	100–200 mg (1½–3 gr)

*Tuinal is composed of equal amounts of quinalbarbitone sodium and amylobarbitone sodium

MINOR TRANQUILLISERS

Minor tranquillisers sedate with less of a hypnotic effect than the barbiturates, and cause no extrapyramidal side effects.

Apart from phenothiazine derivatives such as promazine and properazine, only meprobamate and the diazepine derivatives chlordiazepoxide and diazepam, are of proven value in the treatment of anxiety and tension states.

In many patients with anxiety and excessive tension, these tranquillising drugs are probably no better than, or are even inferior to, the barbiturates. But they are safer in the sense that overdosage with any one of them is unlikely to be fatal, and it is undoubtedly a fact that some patients feel better on one or other of them than on a barbiturate. Addiction is less likely to occur, particularly with the diazepines, although habituation is not uncommon. All will potentiate barbiturates and can therefore be combined with these drugs during semi-continuous narcosis and in combating insomnia. They are also useful during the treatment of alcoholic and drug-dependent patients.

It is difficult to say what, if any, are the special indications for using each of these drugs. Although few controlled comparative trials with them have been reported, clinical impressions are that the diazepines are perhaps superior to meprobamate in their ability to sedate without causing drowsiness, and are less liable to cause side effects.

Controlled trials with all three tranquillisers have produced conflicting results when compared to one another, with phenothiazines, amylobarbitone or a placebo. These conflicting results reflect differences in the design and length of the trial, of dosage and trial material, and they emphasize how difficult it is to prove one drug to be superior to another. Chlordiazepoxide, in a dosage of 10 mg three times a day, may be more effective than amylobarbitone 45–60 mg three times a day. But Raymond[157] used 100 mg amylobarbitone three times a day and found this to relieve anxiety better than meprobamate 400 mg three times a day. Others claim that diazepam is superior to chlordiazepoxide when both are given in a dosage of 10 mg three times a day, but that diazepam has a greater tendency to cause drowsiness. This side effect is all too often ignored in tranquillising drug trials.

The efficacy of a tranquilliser upon anxiety symptoms should be apparent within a few days. It is reasonable to double the dosage if symptoms are unrelieved after a week, and to change the drug if there is no improvement after a further week.

(*a*) *Meprobamate* (*Equanil, Miltown*)

Meprobamate has been in use since 1954, although its popularity has declined since the advent of the diazepines. The drug was developed from mephenesin, with the object of producing a similar but more prolonged muscle relaxant effect. Meprobamate is useful in relieving the muscle-tension symptoms which characterise some anxiety and tension states, although it seems unlikely that its action is primarily upon muscle. Pre-menstrual tension may respond well to the drug given for the week or so preceding menstruation.

400 mg meprobamate at night will often help obsessionally anxious patients to get to sleep. These patients tend to worry about whether or not they will be able to fall asleep. Barbiturates sometimes have the opposite effect to what is intended and merely increase anxiety. Given an hour before bedtime, meprobamate or a diazepine derivative, by diminishing obsessional anxiety and interrupting a vicious circle, will allow sleep to occur. These drugs also have an advantage over barbiturates in that the "hangover effect" sometimes caused by the latter on wakening is absent.

Dosage of meprobamate is 200 mg–800 mg three times a day. The usual dose is 400 mg three times a day.

SIDE EFFECTS

Drowsiness may be troublesome and requires the dosage to be reduced.

Urticarial or erythematous rashes may require the drug to be stopped.

Allergic, toxic reactions occur within forty-eight hours of starting to take meprobamate. It is difficult to estimate the real incidence of these reactions, but Charkes[39] noted one or more in 113 out of 6500 patients receiving the drug. Anorexia, vomiting, diarrhoea, angioneurotic oedema, headaches, fever, proctitis, stomatitis and anuria have been reported. Transient leukopenia and acute non-thrombocytopenic purpura, with peripheral oedema and fever can be serious complications. Very rarely fatal cases of aplastic anaemia and of bullous dermatitis have occurred. Cardiovascular collapse, particularly in older patients, can be alarming.

Addiction and habituation sometimes occur with meprobamate and very large doses may then be taken. Chronic intoxication results in confusion, ataxia and muscle incoordination. The drug should be withdrawn slowly over about a week, for rapidly stopping it can cause delirium, tremor and epileptic fits. Grand mal seizures may in any case be precipitated in patients with epilepsy.

Overdosage will rarely cause death, although suicides have been reported.

(*b*) *Tybamate*

Tybamate is a meprobamate analogue, recently introduced, and does not seem to be superior to meprobamate.

(*c*) *The diazepines*

Chlordiazepoxide (Librium) was introduced into clinical practice in 1960, diazepam (Valium) in 1962. Like meprobamate the diazepines are effective in relieving a variety of anxiety and tension symptoms within a few days of starting treatment, particularly when these are acute rather than chronic.

Special claims have been made for chlordiazepoxide in the treatment of obsessive-compulsive states, but the drug does not relieve these conditions when they exist in their own right and are not secondary to another illness such as depression. However, chlordiazepoxide does seem to be particularly useful in the treatment of phobic anxiety. When phobic symptoms occur against a background of reactive depression the combination of chlordiazepoxide with a MAO inhibitor is sometimes particularly effective (see p. 26). Patients disabled by their symptoms for many years have responded to this drug combination, which to bring about permanent relief may need to be continued for as long as two years.

The diazepines are also useful in the treatment of agitated depression, given *in combination with* an appropriate antidepressant drug and, if necessary, ECT.

Schizophrenic patients with anxiety and tension may also improve when chlordiazepoxide or diazepam is added to their treatment.

A schizophrenic youth of 19, hallucinated and liable to sudden outbursts of terror and violent behaviour, only partially relieved by chlorpromazine and ECT, began to lose these symptoms within a few days of having chlordiazepoxide 20 mg three times a day combined with chlorpromazine.

The diazepines on their own are *not* effective in the treatment of psychotic states.

Chlordiazepoxide is found to be useful in the treatment of alcohol and drug withdrawal states, although it is probably not as effective as chlorpromazine in the treatment of delirium tremens. Larger doses than those required to relieve anxiety must be given, up to 75–100 mg a day on occasions.

There is probably less risk of addiction to one of the diazepines than to meprobamate and the barbiturates. However, addiction in predisposed individuals[91] does occur, and habituation[15] is certainly not uncommon. Toxic psychosis and fits have been reported following sudden withdrawal of diazepam in an addicted woman[76].

Neither of the diazepines is a hypnotic, although in a dosage of 30 mg a day both can produce drowsiness. Chlordiazepoxide 10–25 mg or diazepam 5–20 mg, given an hour before bedtime, will reduce anxiety and allow sleep to occur.

DOSAGE

The usual dosage of chlordiazepoxide is 5–10 mg, of diazepam 2–10 mg, both three times a day. Larger doses will be needed in the treatment of withdrawal states and of schizophrenic anxiety, up to 60–100 mg a day.

SIDE EFFECTS

Drowsiness, dizziness and ataxia are the commonest side effects of the diazepines. Fatigue, nausea, itching, skin reactions, blurred vision, hypotension, loss of libido and impotence have all been reported. Difficulty with micturition may occur, particularly in older patients. Serious side effects are extremely rare. The diazepines are very safe and no deaths have so far been reported from overdosage. They potentiate the action of alcohol and barbiturates.

TRANQUILLISERS WHOSE EFFECTIVENESS IS MINIMAL

(*a*) *Benactyzine* (*Suavitil*)

This drug which, in large doses, produces unpleasant anticholinergic side effects such as dryness of the mouth and difficulty in accommodation, has been claimed to be effective in relieving anxiety

and reactive depression. Clinical evidence for this claim is unconvincing and there seems little justification for its continued use, either alone or in combination with meprobamate (under the trade name of Deprol).

Dosage: 1–4 mg or more three or four times a day.

(*b*) *Hydroxyzine* (*Atarax*)

Dosage: 10–25 mg four times a day.

Side effects are mild and uncommon. They include headache, dry mouth, itching.

(*c*) *Emylcamate* (*Striatran*)

Dosage: 200 mg three times a day.

(*d*) *Prothipendyl* (*Tolnate*)

Dosage: 20–40 mg three or four times a day.

(*e*) *Methylpentynol* (*Oblivon*)

Dosage: 250–500 mg as needed.

Methylpentynol is a short acting sedative and hypnotic which attained popularity ten years or more ago as a preoperative sedative. There is little justification for its use in psychiatry today.

Side effects are unusual. Death from overdosage has been reported.

(*f*) *Bromide*

Although bromides are effective sedatives, they have been included in this section because there is no longer any justification for prescribing them.

The dangers of bromism have long been recognised. There is no justification for using bromide preparations today, yet preparations containing bromide are still prescribed and inevitably cases of bromism still occur.

Bromism is a ubiquitous condition and often mis-diagnosed. Irritability, depression and psychotic states result. There may be an acneiform rash, especially over the face and upper half of the body, a running nose and weeping eyes from increased mucous secretions, halitosis, constipation and gastrointestinal symptoms, anorexia, loss of weight and headache.

The diagnosis, which is often missed because it is not considered, should be confirmed by blood bromide estimations.

TABLE XI

Proprietary medicines containing bromide[139]

Bodryl (Parke Davis)
Bromocarpine (Inter-Alia Pharm.)
Bromoform elixir
Bromo-Seltzer (Thos. Marne Ltd., Hounslow)
Broval (Gedeon Richter Ltd., London)
Calcibronat (Sandoz Products)
Coneuro (Hewlett)
Fennings' Cough Mixture (J. Sanger and Sons, Lancing)
Gower's mixture (various formulae)
Mixture of Potassium bromide (B.P.C.)
Mixture of potassium bromide and nux vomica (B.P.C.)
Mixture of potassium bromide and valerian (B.P.C.)
Dr. Niblett's nerve sedative (C. P. Niblett, London)
Otosedan (Coates & Cooper)
Robuval (Inter-Alia Pharm.)

Obtainable on Prescription Only

S4 Bromevan (Evans Medical Supplies)
S4 Bromidia (Inter-Alia Pharm.)
DD Bromodeine (Crookes)
S4 Carbromal (B.P.C.)
S4 Gabail (Anglo-French)
S1 Gelineau dragées (Wilcox, Jozeau; Mousnier-Delerme, Antony Seine)
S4 Mist. somni opiate (Three-Fifteens)
DD Mulsivin (Rybar)

S1 Schedule 1: poisons. S4 Schedule 4: poisons.
DD Dangerous Drugs.

Preparations no longer in B.P.C. which are still occasionally prescribed

Mixture of potassium bromide and chloral (B.P.C.)
Mixture of chloral and potassium bromide for infants (B.P.C.)
Mixture of gelsemium and hyoscyamus co. (B.P.C.)

HYPNOTICS

Hypnotics are drugs which will induce sleep. The effectiveness of any hypnotic, like sleep itself, is extremely difficult to assess. Hypnotics are administered to many different types of patient under a variety of circumstances and for many reasons. The requirement of a hypnotic will be different for an anxious patient, a geriatric patient, a patient with agitated depression or severe emotional distress, a deluded schizophrenic. So also the effects of any particular hypnotic will differ among different types of patient.

The barbiturates are safe, reliable hypnotics which, when properly used, will generally give a sound night's sleep. In consequence, most clinical trials of new hypnotic drugs use a barbiturate as a yardstick. The use of barbiturates as hypnotics has already been described; by and large they are unsurpassed in their effects. However, there are non-barbiturate hypnotics which on occasion are to be preferred to the barbiturates.

It is sometimes naively assumed that a non-barbiturate hypnotic is "safer", or less liable to cause addiction or habituation, than a barbiturate hypnotic. It needs to be emphasised that drug dependence can occur in predisposed personalities with *any* hypnotic or sedative drug. And any drug, taken in sufficient quantity, can cause death.

Chloral Hydrate

Chloral Hydrate, a chlorinated derivative of ethyl alcohol, was introduced in 1869 and is still one of the safest and most reliable hypnotics available. Given in liquid form, it is rapidly absorbed from the intestine, producing sleep in 10–20 minutes which will last several hours and is not followed by hangover effects. Chloral is metabolised in the liver and kidneys to the active metabolite trichlorethanol.

The main disadvantages of chloral hydrate are its unpleasant taste and liability to irritate the stomach. These may be partially overcome by dilution and the addition of substances such as fruit juice.

Chloral hydrate, in the form of chloral elixir, is particularly useful for inducing sleep in infants and young children. It is also a good hypnotic to give to old patients (liable to become confused with barbiturates), and to patients who sometimes have difficulty in getting to sleep but once off will sleep soundly.

The dose of chloral hydrate is 1·8–3·6 g (30–60 gr) for adults. For children it is usual to give 60–120 mg for each year of their age.

The drug is contra-indicated in serious hepatic or renal failure, and is best avoided in patients with a history of peptic ulcer.

Side effects and toxic reactions are rare. Addiction is unusual but does occur.

A middle-aged woman consumed between 15 and 30 fluid ounces of chloral hydrate a day for several years, and was in the habit of mixing a small glassful with whisky on retiring to bed. This gave her a good ten hours sleep. She felt pleasantly drunk during her waking hours.

Attempts to overcome the disadvantages of chloral hydrate have resulted in the introduction of two derivatives:

(*a*) *Dichloralphenazone* (*Welldorm*) is a combination of chloral with phenazone. It does not have the unpleasant taste and gastric irritant effect of chloral hydrate.

It is prepared in tablets of 650 mg, 1 to 3 of which are be taken at bedtime.

Rarely the drug can cause agranulocytosis (due to the phenazone).

(*b*) *Triclofos* (Tricloryl), marketed in tablets of 500 mg, is also broken down in the body to trichlorethanol. Four tablets or more may be required to produce sleep.

Paraldehyde

Paraldehyde, introduced in 1882, is a safe, quick-acting hypnotic which can be given orally, rectally or by intra-muscular injection. The dose is usually 5–10 ml, but in a psychiatric emergency, which is the only occasion when the drug's administration intramuscularly can be justified, 10–20 ml are usually required.

The disadvantages of paraldehyde are strong. Quite a high proportion of the drug is excreted unchanged in the lungs, so that a vile all-pervading smell occurs throughout the room or ward in which it is used. Intramuscular injection is extremely painful and is liable to cause inflammation or even the formation of an abscess. It is advisable, if a large dose is given, to divide it between two sites.

Paraldehyde is mainly metabolised in the liver and its action may be prolonged in a patient with liver disease. Side effects are rare. Paraldehyde addicts, smelling strongly of the drug, are occasionally still encountered.

The majority of nonbarbiturate hypnotics are relatively new. The chief claims made for them over barbiturates are their supposed greater degree of safety in the event of overdosage, and absence of hangover on wakening. All are probably potentially addictive.

Ethchlorvynol (Arvynol, Placidyl, Serensil) is an oily liquid dispensed in capsules, which is readily absorbed and which produces sleep within 15–30 minutes. Side effects include skin rashes, nausea and vomiting. Dosage is 250 mg–1 g.

Ethinamate (Valmidate, Valmid) is a mild hypnotic quickly producing sleepiness which lasts only 2–4 hours. Dosage is 0·5–2 g.

Glutethimide (Doriden) is related to the barbiturates in structure. Rapidly absorbed from the intestine the drug will produce sleep in 15–30 minutes, lasting for up to six hours or more.

Glutethimide is related to glutamic acid and chemically resembles thalidomide (Distival). However, its metabolism in the body is different from that drug and there is no evidence that it is teratogenic.

Although side and toxic effects are unusual, rare instances of peripheral neuritis and blood dyscrasias have been reported. Addiction and habituation can occur, and withdrawal effects are described. Overdosage with glutethimide has caused deaths.

Dosage is 250–750 mg orally.

Methaqualone (Melsedin) is a quinazoline derivative related structurally to antimalarial drugs. Given in a dose of 150–300 mg orally, the drug will produce sleep in about thirty minutes. No serious side effects or toxic effects have been reported.

Methaqualone, 250 mg, is combined with diphenydramine (Benadryl) 25 mg under the trade name Mandrax.

Methyprylone (Noludar) has a somewhat similar structure to that of glutethimide and its activity is similar.

Side effects, which are rare, include headache, skin rashes, nausea, pruritus and diarrhoea.

Dosage is 200–600 mg orally.

Nitrazepam (Mogadon) is related to the diazepines. In a dose of 5–10 mg it will produce sleep within thirty minutes.

Promethazine (Phenergan) is a useful hypnotic in a dose of 25–75 mg for an adult. As an elixir (10 mg in 7 c.c.) promethazine will produce sound sleep in a child.

Propiomazine (Indorm) was developed from promethazine (Phenergan).

In a dose of 20–40 mg propiomazine will cause sleep after about forty-five minutes.

Side effects resemble those of the phenothiazine derivatives.

Various other hypnotics are available, but have no advantage over those described above. Which drug is used will usually be determined by individual preference and the clinical state of the patient. A barbiturate hypnotic is probably best when anxiety and agitation are marked, combined if necessary with a phenothiazine derivative. In some instances a minor tranquilliser or a sedating tricyclic antidepressant drug such as amitriptyline may prove to be more effective.

CHAPTER V

HALLUCINOGENIC DRUGS

These include drugs such as mescaline, lysergic acid diethylamide and psilocybin.

Hallucinogenic substances have been used for religious and mystical purposes for centuries. The Aztecs employed the sacred mushroom, the Mexicans the dumpling cactus peyotl, both of which are known to contain mescaline. Some medical interest was shown at the end of the last century when Lewen described the mental effects caused by eating these substances. However, it was not until 1943, when Hoffman inadvertently ingested a minute amount of lysergic acid diethylamide (LSD) while investigating that substance and discovered its hallucinogenic properties, that interest was really aroused. Because the mental changes caused by hallucinogenic drugs bear some resemblance to those of schizophrenia, they have been used to investigate psychotic illness and the supposed chemical abnormality thought to be responsible for schizophrenia. At the same time, interest has developed in the therapeutic possibilities of LSD.

LSD has been widely and somewhat indiscriminately used, and has achieved notoriety as a result of newspaper reports of its use among teenagers.

Mescaline and psilocybin have not been used to the same degree and will not be further discussed.

MENTAL EFFECTS OF LSD

The effects of LSD vary to some extent with dosage, the subject's personality, his initial mood, expectation and surroundings. Extremely small doses, 50 micrograms orally, will affect the mental function of most subjects, although some individuals will be virtually unaffected by 200 micrograms or more of the drug. The more common experiences are described below.

Subjective effects begin around 20–30 minutes after swallowing LSD. The first symptom is numbness around the mouth, and this is followed by sensations of dizziness, nausea, palpitations or headache. Perceptual changes develop gradually. Spacial relationships alter and walls and ceilings tilt, recede or advance on the patient. Coloured

patterns and pictures appear on the walls. The subject's body may undergo a sensation of change of shape, of shortening or elongation. Sounds change in quality and quantity, formerly dull or dark colours become dazzling and beautiful, smell and taste become intensified. Synaesthetic reactions sometimes occur, stimulation of one sense organ giving the sensation of a different modality. The sense of time becomes lost or distorted.

Past events are sometimes vividly recalled and relived. Mood varies from calm contemplativeness to profound depression and extreme fear. Paranoid delusions sometimes develop.

> A woman who had taken 200 micrograms of LSD felt that both doctor and nurse were in league against her, were operating a secret apparatus which was affecting her mind, and were putting insects into her bed and over her body. She noticed how the expression on the doctor's face kept changing. She felt extremely thirsty but refused the glass of water offered to her because she knew it to be poisoned. Eventually she lost all control of herself and tried to force her way out of the room.

Thinking becomes less controlled and rational and abstract thought tends to be replaced by concrete thought. Schizophreniac-like thought disorder may develop. The subject may become pre-occupied by hallucinations and fantasy thought, with total loss of insight.

THERAPEUTIC USES OF LSD

Wide and exaggerated claims have been made about the therapeutic usefulness of LSD. It has been used as an abreacting agent. It is claimed to bring repressed material into consciousness, thereby aiding and shortening the time required for psychotherapy[165]. The drug has also been given to patients in group therapy[182].

Proper controlled trials to prove these claims have not been carried out, if only because of the difficulties created by the drug's characteristic and powerful effects. None the less it would be a mistake to ignore the possible therapeutic value of LSD. The drug does enhance suggestibility and may therefore be a useful adjunct to psychotherapy and various forms of aversion therapy. Clinical experience with LSD suggests that it does help some patients with personality disorders and with sexual problems and aberrations.

Remarkable effects are sometimes achieved in individual patients, but it would be wrong to generalise from these results at present. Good results have occurred without any discussion or display of emotion on the part of the patient. In other cases results seem to depend on the emotional reliving (abreaction) of significant past events.

An unmarried intelligent company director of 36 sought treatment for his sadistic sexual behaviour. He had previously received six months' psychotherapy without benefit. After four interviews to establish rapport and elucidate the patient's background, he was given 150 micrograms LSD. After forty-five minutes he became restless, and began to experience a feeling that he was "going backwards in time". He was unable to speak but subsequently described his experience of "going back to the womb and then back beyond that, and fighting with evil suffocating figures". The experiences lasted about four hours and were finally terminated by chlorpromazine 50 mg and amylobarbitone 400 mg given intravenously.

An industrial chemist of 34 was referred because of *phantom limb pain.* Seven years before, his right leg had been amputated above the knee because of a bone sarcoma. There were no complications and he returned home and was fitted with an artificial limb. One year later pain started "in" the amputated leg. He was subjected to various operations on the stump and nerve endings, caudal block, and finally cordotomy, without relief.

He was an obsessional, somewhat inhibited man, who denied that he had any problems. Methylamphetamine, 15 mg intravenously, brought out emotion over his marital state. At the time when pain first began, he was facing the choice of leaving his wife (for whom he felt much resentment) and four children for another woman he loved, or giving up the latter. It was clear that he had never resolved this conflict satisfactorily. He was given LSD on four occasions, the dose being steadily increased from 50 to 200 micrograms. The last two treatments were combined with intravenous methylamphetamine (see below). His pain diminished and was completely gone two months later.

He was seen eighteen months later when pain recurred, this time associated with emotional difficulties at work. Intravenous methylamphetamine brought his resentments to the surface, allowed easy discussion, and pain again disappeared.

Since LSD increases conditionability and heightens suggestibility it could be a useful aid in aversion therapies. Jensen[97,98], for instance, has reported using LSD in the treatment of alcoholism, although he gives the drug at the end of aversion with the aim of increasing the patient's insight into his problems. If, however, LSD is given on the second or third day and following days of aversion treatment, not only may the association between vomiting and alcohol be reinforced but the patient can be more readily "brainwashed" into accepting the idea that he must at all costs avoid "the first drink".

A 42 year old businessman, a compulsive alcoholic, had in the past two years been treated both by psychoanalysis and aversion therapy, with only temporary improvement. He came for treatment reluctantly, at his wife's insistence, and his aggressive manner during the first two days of aversion therapy with apomorphine made the outcome seem

doubtful. He became morose and silent during his third aversion treatment when 25 micrograms of LSD was added. On the fourth treatment day the dose was raised to 150 micrograms. He became tearful, paranoid, and terrified that he was about to be destroyed in some dreadful way. That state lasted for about three hours and during this time he needed a good deal of support. Subsequently he associated the taking of alcohol with his frightening experiences under LSD. Four years later he is still a teetotaller.

A disadvantage of LSD in apomorphine induced aversion is that it may inhibit vomiting. It is sometimes necessary to increase the dose of apomorphine.

DOSE AND METHOD

The dose required to produce effects varies from 25 to 200 micrograms, the average being about 150 micrograms. There is usually little to be gained by increasing the dose beyond 200 micrograms. The drug should, as a general rule, be given only to patients in hospital or under continuous medical supervision since its effects may last up to 24 hours or longer.

A test dose of 50 micrograms in 5 c.c. sterile or distilled (not tap) water is given orally. If there is no reaction the dose is increased by 50 micrograms a day up to 200 micrograms or until effects are felt. It is best to give LSD early in the day so that the reaction will have finished by bedtime. All phenothiazine drugs should be omitted at least twenty-four hours before treatment since their presence will inhibit the drug's effect.

It is essential for the patient always to be attended by a nurse or doctor for as long as effects last. Material coming into the patient's mind may be discussed at the time or the therapist may reserve this for later discussion. The patient is often at his most suggestible at the end of the treatment or during the next day.

The effects of the drug usually begin to lessen after four to six hours, although they may occasionally still be present forty-eight hours later. It is usually advisable to terminate LSD treatment after about four hours, or earlier if the patient becomes too disturbed. Intravenous chlorpromazine 50 mg and amylobarbitone sodium 200–400 mg are an effective antidote. Alternatively 100 mg chlorpromazine and 200–400 mg amylobarbitone by mouth may be sufficient.

LSD's effectiveness is enhanced by combining it with intravenous methylamphetamine, 15–30 mg. This is either given when the patient goes to bed on the night before treatment, or at the same time as the drug. Giving methylamphetamine at bedtime ensures that the patient has a sleepless night, during which time he ruminates about his problems and begins treatment in an anxious and suggestible state of mind.

The treatment can be repeated after an interval of two or three days or longer but there seems little to be gained from giving more than six treatments.

CONTRA-INDICATIONS

Great care is needed over the use of LSD[32]. It is not a drug to be used indiscriminately or incautiously. Depressed patients frequently become more depressed and may attempt suicide. Schizophrenic patients are not helped and may be made worse. Latent schizophrenia, previously unsuspected, can be precipitated into acute schizophrenia. LSD should therefore not be given to patients with bizarre symptoms or whose personality is markedly schizoid.

Manic states can also be precipitated and aggressive psychopathic personalities become difficult to control. True obsessional and compulsive states do not appear to be helped by LSD. Indeed, these patients may feel worse after treatment and will obsessionally ruminate about their experiences with the drug.

Although it is generally agreed that LSD is not a drug of addiction, habituation can occur in abnormal personalities.

CHAPTER VI

DRUG TREATMENT FOR ALCOHOLISM

Treatment of acute alcoholic excitement is similar to the treatment of other states of excitement, but in addition it may be advisable to wash out the stomach. Chlorpromazine 150–200 mg intramuscularly or 50–100 mg intravenously, together with intravenous parenterovite, will usually quickly calm the patient. If excitement continues, chlorpromazine should be repeated. Occasionally it is necessary to give also intramuscular paraldehyde 15–20 c.c. (preferably divided between two different sites), but it is painful and may increase the patient's excitement.

The treatment of delirium tremens is similar to the treatment of other types of toxic confusional states. Chlorpromazine, at least 150 mg three or four times a day, together with amylobarbitone sodium 200–400 mg three or four times a day, may be sufficient to control symptoms. If not, the dosage of chlorpromazine should be doubled and chlordiazepoxide 20 mg three times a day can be added. Intravenous parenterovite should also be given. It must not be overlooked that chlorpromazine itself occasionally increases a patient's restlessness and confusion.

Recently *chlormethiazole* (*Heminevrin*)[70] has been claimed to be effective in the treatment of delirium tremens and confusional states.

Two grams (4 tablets) of chlormethiazole are given orally at the start of treatment, followed by 1g at hourly intervals until deep sleep ensues. Up to 8g or more in 24 hours may be required. Subsequently the daily dosage can be slowly reduced at a rate depending on the patient's state, and stopped after 1–2 weeks. The drug lowers blood pressure and may depress respiration. Side effects include sneezing and itching of the face.

It is important to give tranquillising drugs in adequate dosage to allay the patient's excitement and fear. Frequently too small a dose is given. For instance a middle-aged man admitted with delirium tremens was treated with chlorpromazine 25 mg three times a day and glutethimide 250 mg at night for three days. He became increasingly excited, violent and physically exhausted, and died two days after being transferred to a psychiatric ward. Whether he would have died if he had been heavily tranquillised and sedated on admission, and prevented from becoming dehydrated, is a matter for conjecture. Such a case underlines the need for

large doses of tranquillising drugs, and the danger of this condition.

Once an alcoholic patient has been "dried out" and withdrawal effects have ceased, treatment must be directed at stopping the patient from drinking again.

Aversion therapy is still used in suitable patients, particularly the middle-aged compulsive drinker who has a reasonable amount of drive and ability, and whose tolerance for alcohol is beginning to lessen. The object of aversion therapy is to associate an unpleasant experience with undesirable behaviour, such as alcoholism. In aversion treatment of alcoholism, nausea and vomiting usually constitute the unpleasant experience. This is brought about by giving the patient apomorphine. Alcohol is administered just before he begins to vomit.

However it is not the purpose of this book to describe aversion techniques. These are fully described elsewhere[171].

Dent[56] believed that apomorphine had a specific effect of its own in reducing the alcoholic's tension and craving. Few people today accept this view.

The dose of apomorphine is 3–8 mg ($\frac{1}{20}$–$\frac{1}{8}$ gr) subcutaneously or intramuscularly. In resistant patients the dose can be raised to a maximum of 20 mg ($\frac{1}{3}$ gr). Too large a dose, or abnormal sensitivity to the drug on the part of the patient, may result in excessive depression of the nervous system, cardiovascular collapse, coma and occasionally death.

DISULPHIRAM (ANTABUSE)

Disulphiram was introduced in 1948 for the treatment of alcoholism. Taken by mouth, the drug interferes with the metabolism of alcohol, causing toxic metabolities to accumulate. If alcohol is ingested by a patient who is taking, or who has only just stopped disulphiram, very unpleasant and occasionally fatal results ensue. A knowledge of this, in a proportion of patients, is sufficient in itself to deter them from drinking so long as they continue to take the drug. It is of the utmost importance that the patient should be fully aware of the serious consequences of drinking while taking disulphiram. A patient should never be given the drug unbeknown to him.

DOSAGE AND METHOD

1·0 g a day of disulphiram is taken for three days in two divided doses. The dosage is then reduced to 0·5 g a day and this should be continued for at least six months.

After one week it is often advisable to give the patient a test dose of alcohol, both to ensure that the dose of disulphiram is adequate

and to demonstrate to the patient what will happen if he drinks. Two ounces of alcohol (whisky, gin or an equivalent drink) is usually quite sufficient for this. The patient must be carefully watched for the next two hours. If he is an out-patient he should not be allowed home until all signs of the reaction have finished.

In the presence of disulphiram alcohol causes generalised vasodilatation and a fall of blood pressure. Within about thirty minutes the patient begins to feel hot, breathless, dizzy, and tremulous, Palpitations, a sense of constriction across the chest, nausea, vomiting if much alcohol has been drunk, and headache develop, and the patient may become terrified and convinced he is about to die. Occasionally death has occurred as the result of myocardial infarction. These effects may take several hours to wear off. If the reaction is too severe 1 g of ascorbic acid and an anti-histamine drug, say promethazine 2 c.c. (40 mg), should be given intravenously since part of the reaction is probably due to the release of histamine.

Disulphiram is not employed as a conditioning agent to produce aversion. It is the patient's conscious knowledge of what will happen if he drinks alcohol while taking the drug that acts as the deterrent. Provided the patient is really determined to keep off alcohol, disulphiram is an excellent adjunct to the alcoholic's treatment. But when the patient's motivation is poor, his personality is inadequate, and when follow-up support is lacking, the patient may quickly relapse into his old habits and simply "forget" to take his drug.

SIDE EFFECTS AND CONTRA-INDICATIONS

Side effects are sometimes troublesome. Gastro-intestinal disturbances, an unpleasant taste, halitosis, acneiform eruptions, frequency of micturition, headaches, diminished libido, tiredness, and occasional psychotic episodes may occur. Myocardial insufficiency or liver disease are contra-indications to treatment.

CITRATED CALCIUM CARBIMIDE (ABSTEM)

This acts in a similar way to disulphiram but its effects with alcohol are less severe. Side effects are less common and milder.

The starting dose of Abstem is 100 mg twice a day, subsequently reducing this dose to 50 mg twice a day. Its effects come on more quickly and wear off sooner than those of disulphiram, usually within twelve hours. The reaction of a patient taking the drug to alcohol may be so mild that the test dose of alcohol is sometimes omitted in case this should merely start up a patient's craving again. It is probably advisable to give Abstem rather than disulphiram to the

alcoholic who is likely to drink whilst under treatment. Unstable young alcoholics who impulsively drink a large quantity of alcohol while taking disulphiram may die.

As with disulphiram, caution is needed if the patient has heart disease. Death from coronary thrombosis has been reported in a man on Abstem who was given a test dose of alcohol.

CHAPTER VII

VITAMINS

B group vitamins

Deficiencies of vitamins of the B group in particular are liable to upset the normal functioning of the central and peripheral nervous systems. This is because of the essential part these vitamins play in the metabolism of carbohydrate, and the fact that nerve cells depend mainly upon carbohydrate metabolism for their energy requirements. B vitamins are also concerned with protein metabolism. Aneurine (B_1), riboflavine (B_2), nicotinamide (B_3), and pyridoxine (B_6) are particularly concerned in these vital functions. Cyanocobalamin (B_{12}) and folic acid deficiencies will also disrupt the nervous system, although the mechanism by which this occurs is not yet understood.

Deficiency of vitamin C, the other water soluble vitamin, and the fat soluble vitamins do not in themselves seem to cause abnormal mental functioning and will not be discussed further.

Vitamin deficiencies are nearly always multiple, and treatment should invariably make allowance for this. In poor countries, particularly those where polished rice is the main article of diet, beriberi is still common.

Pellagra occurs in countries where maize makes up the bulk of the diet. In the U.K. beriberi and pellagra are rare and tend to be atypical. Most B vitamin deficiency diseases are either due to a patient eating a cranky or ill balanced diet, or to conditions which interfere with the absorption of food from the gastrointestinal tract or its utilisation.

Psychiatric states can not only result from vitamin B deficiency but may be responsible for the deficiency itself. Bizarre diets are eaten by eccentric, obsessional and lonely people and by some schizophrenics. People with psychotic states of depression may eat nothing but small amounts of starchy food. "Laxative addicts", including occasionally a case of anorexia nervosa, will sometimes purge themselves into a state of deficiency. Many of the cases of B group vitamin deficiency seen in this country are alcoholics who do not eat enough B vitamin containing foods.

Aneurine deficiency causes beriberi, and may lead to polyneuropathy or to the symptoms of Wernicke's encephalopathy.

Nicotinamide deficiency is responsible for pellagra. It may also be a cause of confusional states in old people.

The various neurological and mental disorders which occur in alcoholics are probably the result of multiple vitamin deficiencies, although toxic products from alcohol metabolism, and liver disease, may play some part.

Treatment of all these conditions is the same and consists of giving high potency preparation of mixed B vitamins parenterally. *Parenterovite* contains aneurine 250 mg, nicotinamide 160 mg, pyridoxine 50 mg, riboflavine 4 mg and ascorbic acid 500 mg in 10 c.c. 10 c.c. should be given intravenously daily for seven days. Subsequently B group vitamins can be given by mouth in the form of Becosyn two or three times a day for a month.

Signs of recovery should be apparent in successful cases within two to three weeks, although full recovery may take months and also require physiotherapy and re-educative exercises.

It is advisable to give a week's course of intravenous parenterovite to all alcoholic patients, barbiturate addicts, and psychiatric patients who are senile, confused, or who have lost more than a stone in weight. However, it is not starvation that produces vitamin deficiency states, but ill balanced diets. Patients with anorexia nervosa, for instance, except when they ingest excessive quantities of laxatives, rarely if ever show signs of vitamin deficiency.

In recent years nicotinamide has been claimed to be an effective adjunct to the treatment of schizophrenia. Hoffer and Osmond[88] recommend a minimum dose of 3 g a day orally for at least thirty days. The claims made for the success of this treatment in schizophrenia are unconfirmed, and are regarded with some scepticism by many authorities.

A vast amount of advertising has been devoted to the sale of vitamins. Although deficiency of B vitamins may cause tiredness, loss of appetite, weakness and irritability, in the vast majority of patients these symptoms are due to affective disorders unconnected with vitamins. Yet the medical profession continues needlessly to prescribe vitamins, frequently ignoring the depressive condition responsible for the symptoms.

Vitamin B_{12} deficiency results in pernicious anaemia. In most cases, signs and symptoms of peripheral neuritis are presenting features. But occasionally cerebral involvement occurs first, without the presence of peripheral neuritis. Disorientation, memory loss, depression or lability of mood, particularly when these occur in an elderly patient, may lead to a mistaken diagnosis of dementia. Paranoid features and depression can occur alone and the picture may be mistaken for a psychosis. Blood films will usually confirm the diagnosis. Treatment consists of daily injections of cyanocobalamin (B_{12}) 1000 micrograms for ten days, followed by twice weekly injections for a month, then once a week. Although response may be full and rapid, in most cases it is slow and incomplete.

CHAPTER VIII

ENDOCRINE TREATMENT

In the past endocrine treatments have often been used enthusiastically in various psychiatric conditions, but their success has been limited. It is true of course that deficiency or overactivity of an endocrine gland may bring about psychiatric symptoms which will respond to the appropriate glandular treatment; for instance, mydoedema or hyperthyroidism. It is also a fact that hormone treatments, for instance steroid therapy, are sometimes followed by severe psychiatric disturbances. But in the absence of measurable glandular abnormality there is little place for the majority of endocrine preparations in psychiatric treatment.

THYROID

Thyroid hormone, at one time or another, has been used in the treatment of most psychiatric conditions and subsequently dropped. Only in the comparatively rare instances of recurrent catatonic schizophrenia of the type described by Gjessing, is treatment with thyroid effective. In this condition phases of nitrogen retention correlate with the onset of stupor or excitement. Gjessing[69] showed that by giving thyroxin, which empties the nitrogen stores, the catatonic attack could be prevented. There is no reason to suppose that thyroid in any way helps other types of schizophrenia.

OESTROGEN

Depressive states occurring at the menopause are often associated with hot flushes and symptoms of cardiovascular lability. These symptoms will sometimes respond to small doses of oestrogen, stilboestrol 0·2 mg daily, or to oestrogen-androgen mixtures (Mixogen, Mepilin). But in many instances symptoms will not disappear until the depression is treated satisfactorily. Hot flushes will then either cease, without the need for hormone therapy, or will now respond fully to a short course of stilboestrol.

Oestrogens are occasionally still used in the treatment of male homosexuality and other sexual aberrations, with the object of

suppressing sexual drive. Their value is dubious, although there may be a small place for their use, as an adjunct to treatment, in men whose sexual activities are unacceptable to society. Stilboestrol 1–2 mg a day is usually sufficient. Occasionally a patient may become habituated to stilboestrol.

A male transvestite has taken 5–10 mg stilboestrol a day for several years, on the grounds that the resulting gynaecomastia is desirable. He becomes extremely upset when it is suggested that he should reduce his dosage.

Oestrogens are occasionally helpful in restarting menstruation which has stopped because of emotional conflict. In some cases of anorexia nervosa menstruation may not return for a year or more after weight has been regained. But in general in such instances it is best not to give oestrogens to restore menstruation. Although most amenorrhoeic patients will develop oestrogen withdrawal bleeding, natural menstruation will not necessarily follow. As a result some of these patients with anorexia nervosa become quite severely depressed.

There is no cause for the use of oestrogens in the treatment of schizophrenia.

PROGESTERONE

Progesterone has been widely used for the treatment of pre-menstrual tension. It has also been recommended as a treatment of puerperal psychoses.

Severe pre-menstrual tension can sometimes be disabling. Depression may build up rapidly, almost to psychotic levels, and behaviour disturbances such as kleptomania occur. Salt and fluid should be restricted and a thiazide diuretic given in the latter half of the menstrual cycle. Progesterone 25 mg intramuscularly twice a week, or norethisterone 10 mg orally a day for the last fortnight of the cycle will sometimes reduce tension. But often a careful history will reveal that the pre-menstrual tension is being exaggerated or brought out by an anxiety state or reactive depression. Treatment of the latter will generally cause improvement of the pre-menstrual syndrome.

There is no evidence or reason for believing that progesterone be useful in the treatment of a patient with a *post partum* psychosis. Such an illness is no different from, and requires the same treatment as, a non-puerperal psychosis.

ANDROGENS

Testosterone is only of value in the treatment of impotence if this is the result of testicular failure. In the vast majority of men who complain of impotence there is no testicular abnormality and the cause is psychogenic. Androgens are entirely useless in cases of psychogenic impotence and should not be prescribed. Nor are they of value in the treatment of most cases of frigidity.

Androgens are useful protein anabolic agents, but their use in women is restricted by their virilising effects. Efforts to produce protein anabolic agents without virilising effects have resulted in such steroids as nandrolone (Durabolin) and methandienone (Dianabol).

There is little justification for giving anabolic steroids to psychiatric patients. Treatment needs to be directed to restoring appetite or removing whatever psychological cause is preventing the patient from eating. For instance, once an anorexia nervosa patient starts to eat she will gain $\frac{1}{2}$–1 lb weight a day steadily. It seems illogical and pointless to treat such a patient with an anabolic steroid.

Dehydro-iso-androsterone (Diandrone) was given for a time to immature inadequate schizoid adolescents[166]. The earlier reports of the drug's effects in making these patients more confident and relieving their mood of depression have not been confirmed.

INSULIN

Lastly insulin, although now rarely used to bring about hypoglycaemic comas in the treatment of schizophrenia, is still a useful drug for increasing appetite and weight. Modified insulin, given in conjunction with chlorpromazine, is an effective treatment of anorexia nervosa.

CHAPTER IX

USE OF PSYCHOTROPIC DRUGS IN PREGNANCY

The recent discovery that thalidomide can cause serious congenital malformations has focused attention on the possible danger to the foetus of prescribing drugs to the mother, particularly during the first three or four months of her pregnancy[192].

It is always advisable in theory to stop all drugs to a woman who is trying to conceive. But this may not be so simple as it sounds. Is it justifiable to advise a woman who has had a recent schizophrenic illness and who, against medical advice, has decided to embark on pregnancy, to stop her phenothiazines? Is it always advisable to stop all medication if a patient under treatment inadvertently becomes pregnant? And is a doctor to rely always on reassurance psychotherapy alone for treating the relatively common neurotic and psychosomatic symptoms which occur during pregnancy? Are serious depressive and psychotic illnesses, admittedly rare during pregnancy itself, always to be treated by ECT and perhaps admission to hospital, when drug therapy might be sufficient?

Obviously there is no one simple answer to these questions. Each case needs to be judged in the light of possible teratogenic effects of the drug and the length of pregnancy, of the patient's clinical state, her personality, family and so on. In some instances frank discussion of the problem with husband and wife may be best. In others only harm is likely to come from forcing a decision from the woman and arousing her anxieties.

Remarkably little is known of the teratogenic effects of drugs in man. Congenital abnormalities occur in about 2 per cent[110] of all births, so that individual reports of abnormalities following administration of a drug during pregnancy are not satisfactory evidence. The teratogenic activity of a drug varies widely between different animal species and there is poor correlation between animal experiments and results observed in human infants.

Only insulin and androgens are known to be harmful and definitely contra-indicated during pregnancy. The rate of abortion and congenital abnormality is high when large doses of insulin are given during pregnancy—usually to schizophrenic mothers. Androgens are liable to cause masculinisation of a female foetus.

Apart from obvious congenital abnormalities present at birth, it

is possible that psychotropic drugs taken by the mother during pregnancy may have a more subtle effect upon the foetus and perhaps affect his emotional or intellectual development. Almost no satisfactory work along these lines has been reported, although Ayd has followed up 27 children of mothers treated with chlorpromazine during pregnancy and reported no ill effects[31].

If a sedative or hypnotic drug is required during early pregnancy, one of the barbiturates should be prescribed. There is no evidence, after fifty years use, that barbiturates are liable to cause congenital abnormalities, although in mice there is evidence that they may decrease learning ability in the offspring.

The last few weeks of pregnancy are probably safest, from the teratogenic point of view. When a woman has had previous psychotic illnesses after delivery, or when signs of schizophrenia are still present, it is reasonable to begin prophylactic treatment with a phenothiazine derivative or a tricyclic antidepressant drug, two or three weeks before delivery is anticipated.

A woman of 24 developed schizophrenia after the birth of her first child. She was treated in a psychiatric unit (with the baby) for eight weeks with chlorpromazine and ECT. She was discharged home on trifluoperazine 10 mg twice a day and amitriptyline 100 mg at night. She was able to lead a normal life at home, free of overt symptoms apart from occasionally experiencing "double meanings". Eighteen months later she became pregnant. Drugs were at once stopped and she was seen weekly during her pregnancy. Apart from mild depression during the first trimester she remained well until the last month of pregnancy, when she began to experience fleeting ideas of reference. Trifluoperazine 10 mg twice a day was resumed and increased to 30 mg a day after an easy delivery. Amitriptyline 50 mg at night, 25 mg twice a day, was added when depressive symptoms developed. She did not attempt to breast feed. She returned home after a month and over the next six weeks drugs were reduced to their former level.

APPENDIX I

QUICK GUIDE TO CHOICE OF DRUGS

See Index for page numbers of full discussion in text.

(1) *Anxiety states*	*Treatment*
(*a*) In emergency (acute anxiety)	Sodium amylobarbitone 400–600 mg orally with chlorpromazine (Largactil) 100 mg, or Sodium amytal 400 mg and chlorpromazine 50 mg intravenously or intramuscularly
(*b*) Adequate personality *without* evidence of depression	*Minor tranquillisers:* Diazepam (Valium) 5 mg tds or chlordiazepoxide (Librium) 5–10 mg tds or *Barbiturates:* Nealbarbitone 60–200 mg tds Amylobarbitone 45 mg tds Quinalbarbitone 45 mg tds
(*c*) Adequate personality *with* evidence of depression	Phenelzine (Nardil) 15 mg tds or isocarboxazid (Marplan) 10 mg tds with diazepam 5 mg tds or chlordiazepoxide 5–10 mg tds
(*d*) Basically inadequate personality	Barbiturates generally best
(2) *Hysterical dissociation states*	Intravenous sodium amylobarbitone 60–100 mg
(3) *Obsessional-compulsive states*	
(*a*) Without accompanying depression	Chlordiazepoxide 5–10 mg tds or trifluoperazine (Stelazine) 1 mg tds

(*b*) Accompanied by depression	Phenelzine 15 mg tds or isocarboxazid 10 mg tds with chlordiazepoxide 5–10 mg tds
(4) *Depression*	
(*a*) *Reactive* (anxiety symptoms in evidence)	A monoamine oxidase inhibitor plus tranquilliser. Phenelzine 15 mg tds or isocarboxazid 10 mg tds and chlordiazepoxide 5–10 mg tds or diazepam 5 mg tds
(*b*) Endogenous	Tricyclic antidepressants such as imipramine (Tofranil) or amitriptyline (Tryptizol), each 50 mg tds
(*c*) Agitation prominent	Amitriptyline 100 mg o.n. 25 mg b.d. with phenothiazine tranquilliser such as trifluoperazine 1 mg tds or chlorpromazine 25 mg tds (Occasionally, in unresponsive patients, amitriptyline may be combined with a monoamine oxidase inhibitor)
(*d*) Retardation prominent	Imipramine 50 mg tds
(*e*) Paranoid symptoms prominent	Imipramine 50 mg tds and trifluoperazine 5 mg tds
(5) *Manic Illness*	
(*a*) Acute mania	Haloperidol (Serenace) 5 mg intravenously followed by 6 mg orally b.d., with chlorpromazine 200 mg, if necessary three or four times a day
(*b*) Subacute mania	Haloperidol 3 mg–6 mg b.d. and/or chlorpromazine 50–100 mg tds, Lithium carbonate 1–1·5 g a day
(6) *Schizophrenia*	Phenothiazine derivatives in large dosage
(*a*) Agitation prominent	Chlorpromazine 100 mg or more tds
(*b*) Apathy prominent	Trifluoperazine 5–10 mg tds

(7) *Confusional States*	Chlorpromazine 100 mg (or more) tds orally or parenterally (with sodium amylobarbitone 200 mg (or more) tds if necessary)
(8) *Delirium tremens*	
(9) *Withdrawal States*	High potency vitamins should be given concurrently

With large doses of phenothiazine derivatives or haloperidol it is always advisable to give an antiParkinsonian drug such as benzhexol (Artane) or orphenadrine (Disipal) in addition.

APPENDIX II

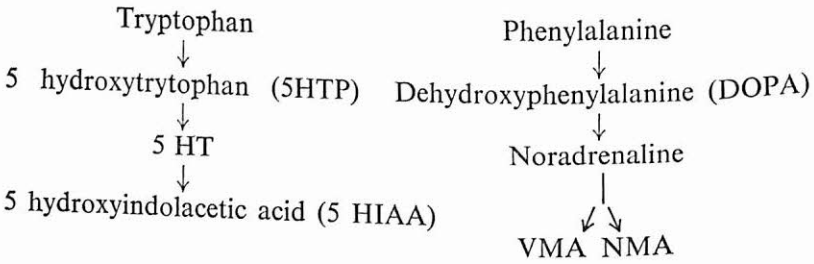
BIOCHEMICAL MODES OF ACTION OF THE MONOAMIDE OXIDASE INHIBITORS AND TRICYCLIC ANTIDEPRESSANT DRUGS

The action of drugs on the central nervous system is complex and still far from being understood.

There has been considerable interest and speculation concerning the possible importance of brain monoamines over the past twelve years, particularly 5–hydroxytryptamine (5 HT), noradrenaline, and its precursor dopamine.

Noradrenaline and 5 HT occur in high concentration in the hypothalamus, and are virtually absent from the corpus striatum; in the case of dopamine these distributions are reversed. Adrenaline is present in low concentration in the brain.

The metabolic pathways of these monoamines is shown below.



It is thought that these monoamines exist in stored and free forms. In the stored form they are contained in special cell granules or nerve vesicles (storage organelles), where they are inactive and are protected from metabolising enzymes such as monoamine oxidase (MAO). On nervous stimulation the monoamines are released from their stores.

Part of the stored monoamines is situated close to structures containing MAO. When released by nervous stimulation, "free" noradrenaline is immediately metabolised and inactivated by the MAO. But part of the stored monoamine is probably situated close to nerve endings, away from MAO containing sites. Noradrenaline released from this store is not therefore destroyed, and activates

nearby adrenergic receptors. 95 per cent of this free noradrenaline is inactivated by being reabsorbed into the storage pool.

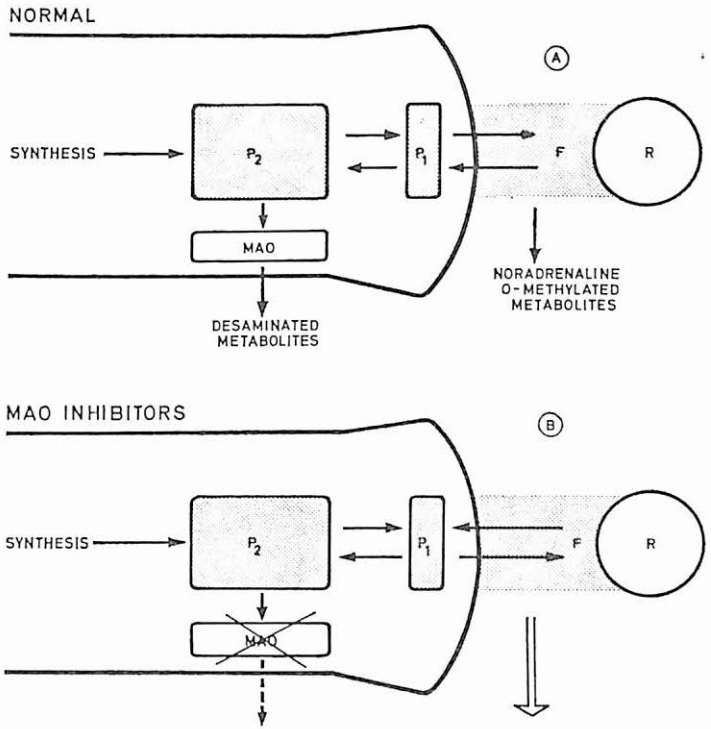


Fig. 1. Model of Sympathetic nerve ending with the various monoamine pools and hypothetical action of MAO inhibitors on the amine pools. P_1 = superficial monoamine store; P_2 = deep monoamine store; F = free monoamines; R = adrenergic receptor; MAO = Monoamine oxidase.

MAO inhibitors, drugs which inactivate MAO, will naturally raise the concentration of monoamines in the brain.

The concentrations of 5 HT and noradrenaline can also be raised by giving the precursors of these monoamines, 5 HTP and DOPA.

On the other hand reserpine and benzoquinolyzines cause monoamines to disappear from the brain. These drugs interfere with and release monoamines from their fixed sites, and also prevent their reabsorption.

Since reserpine produces sedation and MAO inhibitors cause excitement, it is suggested that sedation is due to depleted brain monoamines, excitement to accumulation of these substances. There is disagreement as to which amine is concerned. Additional evidence for this theory is that after pretreatment with a MAO inhibitor

reserpine no longer produces sedation but may induce excitement, owing to an increase of free monoamines.

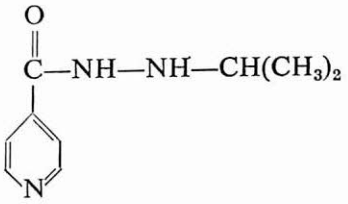
Amphetamine acts by releasing active noradrenaline and by blocking cellular uptake of noradrenaline. It has been suggested that the depressed mood which sometimes follows amphetamine induced euphoria is caused by temporary depletion of noradrenaline stores available to continued release.

Imipramine, and perhaps other tricyclic antidepressants, act by interfering with reabsorption of noradrenaline into fixed sites. The drug therefore raises the concentration of free noradrenaline at adrenergic receptors.

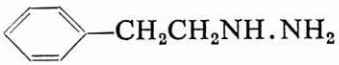
APPENDIX III

STRUCTURES OF ANTIDEPRESSANT DRUGS

Iproniazid

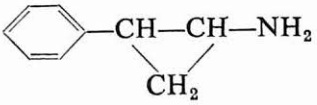


Phenelzine

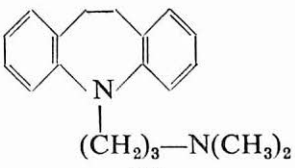


Isocarboxazid

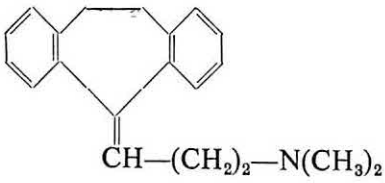
Tranylcypromine



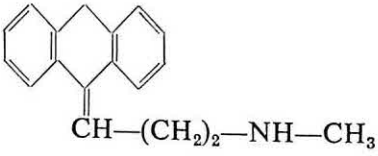
Imipramine



Amitriptyline



Nortriptyline



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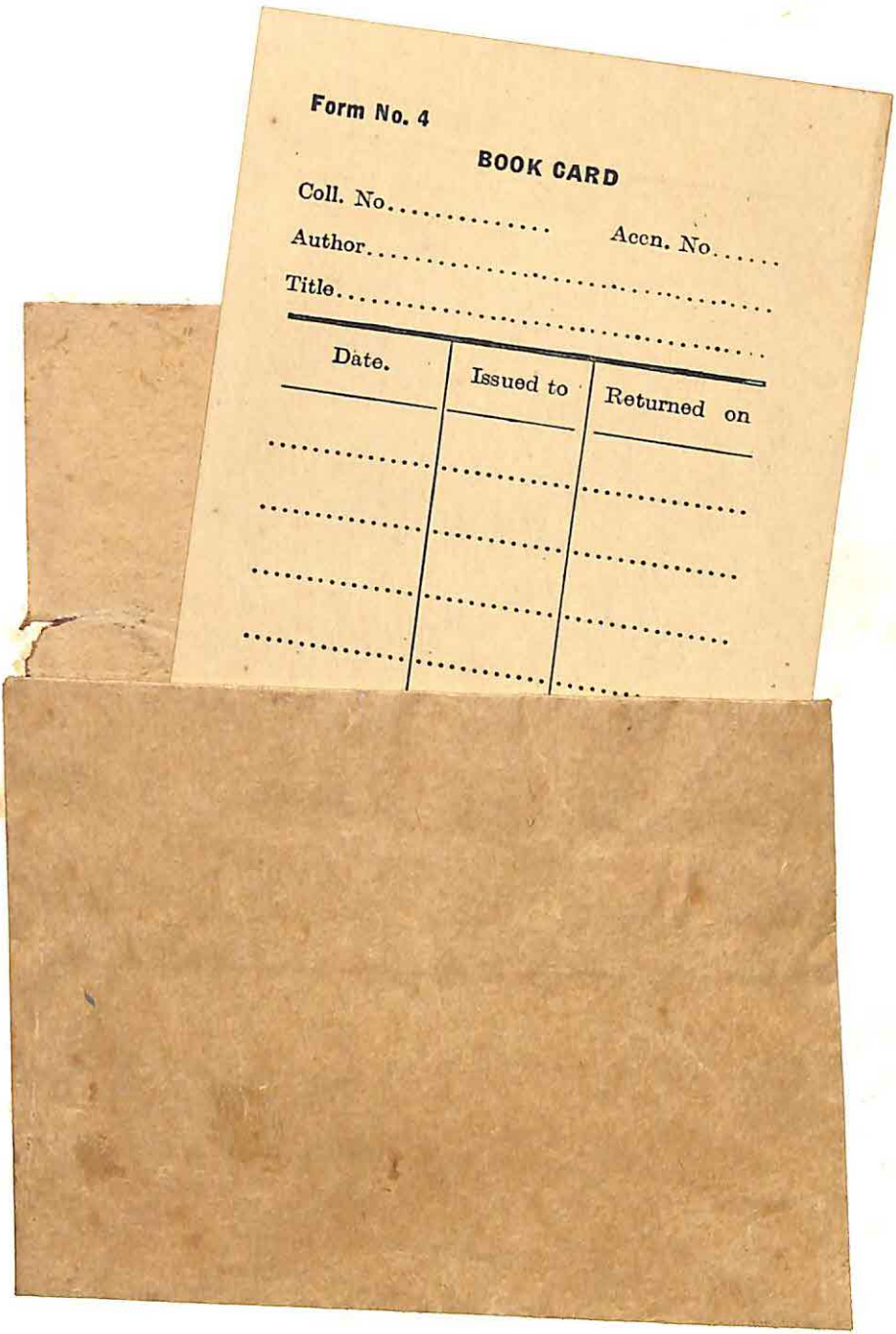
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